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A clinical study of the neuropsychological outcome comparing Cardioplegic arrest Versus Intermittent cross-clamp fibrillation as myocardial protection techniques in coronary artery bypass grafting surgery

by

Dr.Sujeeth Harsichandra Suvarna

MBBS, FRCS (Ir)

Unit of Health Psychology and Department of Cardiothoracic Surgery
University College London Hospitals
London

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Abstract

Objective

A randomized clinical trial seeking evidence as to whether cardioplegic arrest (CA) or intermittent cross-clamp fibrillation (ICCF) method of myocardial protection technique would have any effect on the post-operative neuropsychological outcome in patients undergoing elective coronary artery bypass grafting (CABG) surgery.

Methods

One hundred and ninety-five patients were randomized to either CA or ICCF as the method of myocardial protection technique. Cerebral microemboli (ME) during surgery were recorded by transcranial Doppler monitor over the right middle cerebral artery. Evidence of cerebral impairment was obtained by comparing the patients' performance in a neuropsychological test battery (9 tests) administered 6-8 weeks post-operatively with their pre-operative scores.

Results

The groups proved well balanced in pre-operative variables. During cardiopulmonary bypass (CPB) the median number and range of microemboli was 110 (1-1306) in the CA group compared to 105 (9-1757) for the ICCF group ($p<0.567$). One hundred and seventy-seven patients completed all the neuropsychological tests. The difference between the two groups did not reach significance ($p=0.326$, 2 tailed t test).

Conclusion

Given the similarity of effect in CA and ICCF techniques on the generation of ME and neuropsychological outcomes during CABG surgery, this investigation suggests that other than the myocardial protection technique analysed, there are other multiple causes that need to be studied.

List of Abbrevations used

ACT: Activated Clotting Time

APOE: Apolipoprotein E

ASE: American Society of Echocardiography

BP: Blood Pressure

CA: Cardioplegic arrest

CABG: Coronary artery bypass grafting surgery

CBF: Cerebral Blood Flow

CES-D: Centre for Epidemiological Study OF Depression

CKMB: Creatinine kinase isoenzyme MB

CPB: Cardio pulmonary bypass

CRT: Choice reaction test

CT: Computed tomography

CVA: Cerebrovascular accident

DP: Digital palpation

EAU: Epiaortic ultrasonography

ECC: Extracorporeal circulation

EVA: Etude du Vieillissement Artériel

FAPS: French study of aortic plaque in stroke

GPD: Grooved Pegboard – Dominant

GPND: Grooved Pegboard – Non Dominant

HITS: High intensity transient signals

ICCF: Intermittent cross-clamp fibrillation

ID: Internal Diameter

LCT: Letter cancellation test

LNNB: Luria Nebraska neuropsychological battery

LV: Left ventricular

MAP: Mean arterial pressure

MCA: Middle cerebral artery

ME: Microemboli

MRI: Magnetic resonance imaging

NART: New Adult Reading Test

NORG: Neurologic Outcome Research Group

NP: Neuropsychological

NVRM: Non-Verbal Recognition Memory Test

OR: Odds ratio

PTCA: Percutaneous Transluminal Coronary Angioplasty

PVD: Peripheral vascular disease

R-AVLT: Rey Auditory Verbal Learning Test

ROOBY: Revascularization On versus Off Bypass

RR: Relative risk

SCAD: Small capillary and arterial dilatation

SD: Standard Deviation

SDRT: Symbol Digital Replacement Test

SPSS: Statistical Package for the Social Sciences Software

STAI: Spielberger State and Trait Anxiety Inventory

TCD: Transcranial Doppler ultrasonography

TIA: Transient ischaemic attack

TOE: Transoesophageal echocardiography

TMTA: Trail making A

TMTB: Trail making B

TnI: Troponin I

TnT: Troponin T

WAIS-R: Wechsler adult intelligence test-revised

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Articles published-Abstracts

An intraoperative assessment of the ascending aorta: a comparison of digital palpation, transesophageal echocardiography, and epiaortic ultrasonography [207].

Suvarna S, Smith A, Stygall J, Kolvecar S, Walesby R, Harrison M, Newman S.

Source

Department of Cardiothoracic Surgery The Heart & UCL Hospitals, London, United Kingdom.

Abstract

OBJECTIVES:

There are a number of techniques available to assess the aorta for atheromatous disease in the intraoperative period. This study compared the relationship among the findings of digital palpation (DP), transesophageal echocardiography (TEE), and epiaortic ultrasound (EAU) in the detection of atheroma in the ascending aorta.

DESIGN:

A prospective, observational study.

SETTING:

A single-institution, cardiothoracic specialty hospital. Participants: One hundred fifty-four patients undergoing elective cardiac surgery.

INTERVENTIONS:

The ascending aorta of patients undergoing elective coronary artery bypass surgery was assessed for atheroma by means of the 3 techniques. Atheroma was scored as present or absent. The sensitivity and specificity of the techniques were compared.

MEASUREMENTS AND MAIN RESULTS:

Assuming EAU provides the "gold standard," the sensitivity of both TEE and DP were low. Digital palpation identified only 20 patients (12%); TEE 31 patients (20%); and, in contrast, EAU detected atheroma in 81 patients (53%). There were 3 and 6 false-positives by DP and TEE, respectively.

CONCLUSION:

Assuming EAU as the "gold standard" to detect atheroma, this study has shown that when assessing the ascending aorta neither DP nor TEE appear sensitive. This study supports the proposal that detection of atheroma should be performed by EAU.

Effect on the brain of two techniques of myocardial protection [208].

Stygall J, Suvarna S, Harrington J, Hayward M, Walesby RK, Newman SP.

Source

Unit of Behavioural Medicine, UCL, Charles Bell House, London W1W 7EJ, United Kingdom.

Abstract

This study compared the occurrence of intraoperative microemboli and postoperative changes in neuropsychological performance in 195 patients undergoing coronary artery bypass grafting who were randomized to intermittent crossclamp fibrillation or cardioplegic arrest. Cerebral microemboli were recorded from cannulation to 15 min after decannulation, using transcranial Doppler in 166 patients. Microemboli in relation to 9 surgical events were also noted. Neuropsychological change scores were obtained by comparing cognitive performance preoperatively with that at 6-8 weeks after surgery. The median number of microemboli detected was 105 (range, 9-1,757) in the fibrillation group, and 110 (range, 1-1,306) in the cardioplegia group, with no significant difference between groups. There was also no significant difference between groups in the generation of microemboli during any of the surgical events. Neuropsychological tests were completed postoperatively by 177 participants, with no significant differences in performance found between the 2 groups. Given the equivalence of the effect of intermittent crossclamp fibrillation and cardioplegic arrest on microemboli and neuropsychology, consideration of which form of myocardial protection to employ should perhaps focus more on which method affords most protect

Introduction

Coronary artery bypass graft (CABG) surgery is one of the most commonly performed cardiac surgical procedures worldwide, intended to treat ischaemic heart disease and alleviate angina pectoris. Despite advances in surgical procedure, cerebral injury is still an important complication after CABG .The two main clinical manifestations range from stroke to a subtle decline in neuropsychological (NP) performance. Roach et al (1996) from a multicenter study classified these cerebral injuries into two types[1]; Type 1 injury includes stroke, transient ischaemic attack, and coma (incidence 1.5% to 5.2%) [2]. Type 2 injuries are subtler and include impairment of neuropsychological (NP) deficit (incidence that varies from 20% to 80%) [3].

Neuropsychological (NP) deficit is more common and is defined as an impairment involving any or all of concentration, memory, learning or the speed of mental and visuomotor response. These NP deficits can be classified as short- (immediately after surgery) and long-term (1-5 years post surgery) NP deficits following CABG, but the pathophysiology of these changes remains incompletely understood. But with improvements in protection techniques the risk of adverse NP outcome has improved to about 20% and these incidence of deficits vary according to the different methods and timing of measurements used in each study[4]. The cause of early NP deficit tends most likely to be mutifactorial and may include from microemboli (ME), hypoperfusion, and other factors resulting during surgery, while late deficits occuring 1 and 5 years after surgery tend to be secondary to cerebrovascular disease among CABG patients[5]. Following three studies 1) Selnes et al (2001)[5], 2) Newman et al (2001)[6], and 3) Stygall et al (2003)[7] have shown that long term NP deficits are seen persisting as long as 5 years. These incidences vary with published accounts due to methodological issues, including the timing of testing.

Although various factors and mechanisms may contribute to these NP deficits during CABG surgery, cardiopulmonary bypass (CPB) is considered to be one of the most significant causes[8]. Despite these findings, some recent studies have shown that such NP deficits are also seen in patients where CPB is not used[9].

But, this thesis focuses mainly on the NP deficits caused by myocardial protection techniques such as cardioplegic arrest (CA) or intermittent cross-clamp fibrillation (ICCF) during CABG surgery. Apart from different myocardial protection techniques NP deficits are also known to occur due to surgical handling of the ascending aorta leading to the release of microemboli (ME) from atherosclerotic plaques present in the ascending aorta[10]. Also, in this chapter we will look into various aetiological factors to see if they have some influence on post-operative NP outcomes especially during CABG surgery using the standard CPB technique comparing the two myocardial protection techniques. It is only since cardiac surgery became an extremely common and safer procedure[10] in the 1970s that attention was able to shift from mortality rates to more subtle measures of outcome such as neuropsychological (NP) function.

However, the relationship between NP deficit and ME are still not clear with some finding a relationship [11,12,13] and others none[14,15]. With the possible incidence of atherosclerotic disease being present in this sub-group of patients undergoing CABG the identification of these sites and severity of atheroma in the ascending aorta during the intra-operative period is now hypothised as an important prologue in minimizing the incidence of adverse cerebral and NP events in the intra-operative period.

Therefore, in this thesis I have included the screening of the ascending aorta along with the detection through the transcranial Doppler (TCD) ultrasonography, of ME, which may occur during the CPB, comparing the two different myocardial protection techniques using CA and ICCF techniques. This chapter will also describe the development of NP testing, explain how it is best carried out, summarise the main findings relating to cardiac surgery and discuss some of the complex methodological issues involved.

Chapter 1

Various factors that may influence the neuropsychological outcome after coronary artery bypass graft surgery

1.Various factors that may influence the Neuropsychological outcome after Coronary Artery Bypass Graft surgery

1.1. Coronary Artery Bypass Graft surgery

With over one million patients undergoing Coronary artery bypass graft surgery (CABG) annually, the incidences of cerebral injuries especially the occurrence of neuropsychological (NP) deficits would also tend to rise. A correlation between the severeity of coronary artery disease and the extent of atherosclerosis in the brain is increasingly becoming a common finding. Elderly patients over the age of 70 years are likely to have vascular disease of the cerebral circulation and therefore maybe more susceptible to microembolic injury than the younger patients.But, despite recent advances in surgical and anaesthetic techniques, causes leading to NP deficits are thought to be multifactorial and the pathophysiology of these changes are still not understood fully. Evidence is now emerging, however, that neurosychological test variables, patient-related factors and procedural related variables might have a more important role in post operative neuropsychological decline than previously thought.

1.2. Methods of Neuropsychological Testing

In a clinical setting a psychologist would conduct the standard clinical NP assessment of an individual patient over one or two test periods totalling between about two and five hours. The patient is given a comprehensive battery of up to 25 standardised tests with the aim of identifying and localising a brain lesion, assessing the degree of cognitive disturbance in patients with known brain lesions or in order to distinguish between neurological and psychiatric symptoms[16]. The NP assessment of outcome following cardiac surgery differs from this standard assessment in several ways.

Firstly, assessments must be performed both prior to and then following surgery, rather than the single assessment thus enabling comparisons to be made between the patients own baseline score pre-operatively to post-operative performance. The purpose is to measure change in performance over time. Time constraints only allow about one hour for each of the pre-operative and post-operative tests. Therefore, in order to perform as many tests as possible and so be as comprehensive as possible in testing different cognitive domains, relatively short tests must be selected. Investigators have used between 1 and 14 tests in various studies. The fact that the test will be repeated shortly afterwards demands that the test should have a minimal learning effect. Parallel forms of the same test may be used to reduce learning effects. If the tests were too easily learnt this would decrease the sensitivity of post-operative testing. Some degree of learning is inevitable with most tests and it is expected that the majority of patients without impairment will show an improvement in neuropsychological test performance post-operatively. As learning is inevitable, it is best taken into account using Z change scores (discussed in later chapter). It can therefore be seen that the battery of tests one uses to assess patients before and after cardiac surgery is a compromise between wishing to be as comprehensive as possible while completing testing in about one hour.

Previous incidence studies were designed to assess what affect cardiac surgery had on cognitive function. These previous early studies used a single group assessed on at least two separate occasions. This work established that a proportion of patients do show a post-operative neuropsychological decline but the incidence varied widely. While it has been suggested that such a variety of results could be due to an inherent problem of neuropsychological testing, the variability is no greater than that reported for post-operative strokes[17]– a related problem which is often perceived as a more reliable outcome measure as it has overt clinical signs and consequences. It is worth considering the reasons for variability between results of these incidence studies. The factors that will affect results are test, patient, study design and data analysis variables.

1.2.1. Neuropsychological Test Variables

As has already been mentioned, neuropsychological testing in cardiac surgery is a compromise between being exhaustive in assessing cognition and being able to perform the tests in the limited time available. The more tests that are used, the greater will be the probability of detecting a lesion because more domains are being tested. However the potential problem of using too many tests is that some may test the same domain and result in a deficit appearing worse than it actually is. The sensitivity of the tests used in neuropsychology test batteries has improved as the study of NP outcome has been refined. The early studies used intelligence tests or tests such as the Mini Mental State Exam. Although these are highly reliable they are relatively insensitive[18] and a number of tests have now been specifically chosen for use in cardiac surgery as per the Statement of Consensus recommendation[19]. This core battery minimally includes the Rey Auditory Verbal Learning Task, the Trail Making Tests A and B, and the Grooved Pegboard. These tests are now widely used, easy to conduct, well-normalised, and sensitive to cerebral damage.

The way in which tests are administered is highly important but it is rarely mentioned in publications. To ensure reliability of assessments it is preferable that the same psychologist does the pre-surgery and post surgery tests in the same environment. Factors such as noise and lighting may have effects upon test results. Also it is important that the patient can practise tests and so be fully aware of what is expected with each test and perform to the best of his/her ability.

1.2.2. Neuropsychological Stastical Analysis variables

The statistical analysis of NP data may have a significant influence on the incidence of neuropsychological deficit found. Methods of analysis have evolved in an effort to be more sensitive but there is no universally accepted method. Some investigators have been criticised for using as many methods as possible to analyse their results and then presenting the method which yields the most significant result. It is therefore important to define the type of analysis to be used when designing a trial and deciding on sample numbers. One has to choose a method of analysis to use before starting a trial and then keep to this plan.

The earlier, descriptive studies, which involved a single group of patients undergoing cardiac surgery, examined NP change from before to after surgery. The change in performance was analysed as group comparison or individual comparison. Group comparison consists of pooling data and determining whether the group as a whole has altered its performance. In order to detect a deficit the mean of the group has to drop significantly. This makes the assumption that most patients will experience a deficit, but in fact only a minority of patients are likely to. Also it takes no account of the potential learning effect of the tests. The patients who improve through learning may mask the patients who deteriorate. This type of analysis therefore has flaws. Probably superior for single group studies are individual comparisons which examine individual changes with each patient acting as his own control. The main problem that then arises is how to define what extent of neuropsychological deterioration constitutes a deficit. There is still no consensus as to what constitutes a deficit. However most researchers accept that deterioration on at least two tests is required as a poor performance on only one test may simply reflect a lapse in performance. (Although it may also mean that only one cognitive domain has been affected). A deficit has usually been defined in standard deviation (SD) terms with most investigators classifying a deficit as a drop in one or more SDs from the pre- operative to post-operative levels. The SD may be a population SD when standardised tests are used or it may be calculated from the pre-operative performance in an attempt to establish a notional standard score for the group being examined. However this method may become insensitive because it applies a fixed amount of deterioration to all individuals regardless of their absolute levels. Another similar approach is to take a drop in 20% in a test performance to reflect a significant deterioration. This therefore overcomes the problem by taking a proportional drop in performance to define a deficit.

When interventional studies are analysed, there are again a number of approaches. In these studies, there are two or more groups having cardiac surgery with or without a particular intervention. There are now several ways in which group comparisons can be performed in interventional studies. One alternative method, the individual incidence approach, used by Pugsley[20], and described by Newman[21] enables a comparison to be made between the groups in terms of the number of individuals showing a deficit. A standard deviation (SD) unit is first calculated from all the patients' preoperative scores. One then calculates the change in score for each patient for each test. In an identical manner to the methods of descriptive studies, a deficit in a test is said to occur when the patient's individual score in a test decreases by more than one SD from their preoperative score. A patient has a significant deficit if this occurs in 2 or more tests. One then compares the incidence of deficits between two or more groups. This conventional definition was widely applied in research until a few years ago when some drawbacks became apparent. In addition to the problem of arbitrarily defining a deficit, as explained above, it also has also become less sensitive. This method classifies a patient in a binary fashion as either having a deficit or not having a deficit with no intervening scale. Sensitivity is therefore reduced when analysing by incidence of deficits. As the incidence of NP deficits has declined with improvements in surgical and perfusion and anaesthesia practice, the lack of sensitivity has become more apparent. Another criticism of the incidence of deficits method is the phenomenon of "regression towards the mean". Regression towards the mean is the statistical observation of a biological phenomenon whereby extreme baseline scores tend to become less extreme on repeated testing. In the case of NP testing before and after cardiac surgery it has been argued that those with higher preoperative scores are more likely to regress towards the mean and show an apparent, although not real, deterioration. Conversely, those with low scores preoperatively would improve in a similarly spurious way if they regressed towards the mean. However this theoretical argument can be refuted by the facts observed after cardiac surgery which are the exact opposite: those patients with better preoperative NP scores tend to deteriorate less[22].

More recently Arrowsmith et al[14, 23, 24, 25] have introduced "Z", or "change" scores and these are now becoming an additional accepted way of analysing NP data with greater sensitivity. To calculate a Z score each patients' test score on each occasion is converted into a standardised score by dividing by the SD of the preoperative group performance of all patients in a study. A change score is then calculated for each patient by subtracting the postoperative standardised score from the preoperative standardised score. One can then calculate a mean of the change scores for each group. This method is more sensitive because it is a continuous change score without absolute cut offs. It also allows group comparisons which take into account potential learning affects. Since Z scores have only recently been introduced, it is a more sensible approach to analyse NP results using deficit scores as well as Z scores. This has the advantage of making it possible to compare incidence of deficits to previous studies.

1.3 Patient-related varaibles

There are a number of patient-related variables that could explain the differences.

1.3.1. Age

The age group of patients undergoing CABG surgery in the United Kingdom has been increasing steadily over the past decade as per the National Adult Cardiac Surgical Data base report 2011-2012[26]. At present nearly a quarter of all patients are above the age of 70 years and out of that 8% are over the age of 75 years. There is considerable evidence that age is associated with NP outcome following CABG surgery. Older patients have a worse outcome[21,27,28,29].

This may be due to more ME release in older patients[30] or the fact that with the increase in the mean age, the cerebral blood flow auto regulation on CPB may be impaired in these sub-groups of elderly patients[21]. This will be further discussed in this chapter as well as subsequent chapters.

1.3.2. Gender

Overall more male patients undergo CABG surgery when compared to women. But there is some evidence that women are at higher risk than men for NP deficits after cardiac operations, perhaps because more have pre-existing hypertension than men. A study by Hogue et al[31] assessed 117 patients (79 men and 38 women) undergoing cardiac surgery using a battery of neurological tests including a broad array of cognitive domains including attention, memory, executive function and psychomotor processing speed. The tests were conducted a day before the operation and 4 to 6 weeks post-surgery. Although the frequency of NP outcome was similar between women and men, women appeared to be more likely to suffer injury to brain areas sub-serving visuo-spatial processing. The same author in randomized study found no difference in NP outcomes using 17beta-estradiol in postmenopausal women[229].

1.3.3. Left ventricular dysfunction

Left ventricular (LV) dysfunction is known to be associated with increased operative and post-operative mortality in patients undergoing CABG surgery. It might, therefore, be expected that there may be an association between poor left ventricular function and poor post-operative NP outcomes because of post-operative low cardiac output status. Depressed LV function may thus lead to intra-operative haemodynamic instability and low-output state directly disturbing normal cerebral perfusion and contributing to neurological events. Blachly and colleague in 1966 showed that post-operative neurological symptoms such as confusion and hallucinations were related to low post-operative cardiac output[32]. Poor LV function has been named as one of the predictors of causing early NP deficits in a more recent study[33].

1.3.4. Pre-existing cerebrovascular disease

Harrison et al in 1989[34] investigated the relationship between pre-existing cerebrovascular disease and NP dysfunction. A series of 78 patients undergoing CABG surgery were studied prospectively to see if angiographic evidence of cerebrovascular disease demonstrates any correlation with the incidence of NP dysfunction at 8 days or 8 weeks after surgery. Out of 78 patients, only 47 had complete angiography and NP assessment. In 51% there was evidence of vessel wall disease and in 17% there was stenosis of at least one carotid artery in the neck, of which only one patient had severe narrowing. In total, 77% of these 47 patients showed an NP deficit as defined by a significantly reduced score in at least 2 of 10 tests administered at 8 days after surgery. At 8 weeks post-surgery, 36% still had deficit. Their study did not show any significant correlation between angiographic evidence of carotid artery disease and the development of NP deficit. They conclude from their results that NP deficits are common with or without carotid artery disease, with or without frequent episodes of hypotension and with or without evidence of pre-existing cerebrovascular insult. This implies that cerebrovascular disease is not a major factor in the development of post-operative NP deficit. However, this study was underpowered with only a small number of patients having severe carotid disease while transcranial vessels were not examined.

1.3.5. Hypertension

Hypertension is a major risk factor for coronary artery disease and cerebral injuries. Hypertension is usually associated with impaired cerebral blood flow regulation to the brain and when in the presence of other co-factors such as age and diabetes mellitus, peripheral vascular disease can cause damage to the brain, heart, kidney and other major organs in the body. Therefore, the relationship between hypertension and NP deficits has been the topic of interest for many decades.

Cross-sectional, population based studies have had mixed findings regarding hypertension and cognitive outcome. Some studies by Farmer et al, 1985 and Scherr et al, 1991 have found minimal or no relationship[35,36], whereas Elias et al in 2003 found an association with higher blood pressure[37] and Guo et al, 1997 noted an association with lower blood pressure[38].

Longitudinal studies including the Framingham heart study and the Etude du Vieillissement Artériel (EVA) study indicate that NP performance persists or worsens over time among hypertensive patients[39,40,41].

1.3.6. Obesity

The relationship between obesity and vascular disease is well known. It plays an important role along with hypertension, diabetes and hypercholesterolemia in increasing the overall risk factors for any neurological injuries. Eighteen-year surveillance data collected from the Framingham heart study by Elias and co-workers, 2003 showed obesity and hypertension to have adverse effects on the cognitive outcomes in the general population[37].

1.3.7. Diabetes mellitus

The mechanisms of post-operative NP deficit in patients with diabetes following CABG surgery are not fully understood[225].

Miles and Root in 1922 conducted an NP study because of complaints of memory loss and difficulty in concentrating in diabetic patients. They compared diabetic and non-diabetic patients. Their work suggested that diabetic patients might experience a significantly greater impact on cognitive function[42].

The human brain is almost totally dependent on a continuous supply of glucose, deprivation of which rapidly causes malfunction. In the brain there are regional differences in the susceptibility to neuro-glycopenia with the cerebral cortex being most sensitive while deeper structures are more resistant. Repeated episodes of hypoglycaemia do lead to cognitive impairment[43]. There is little information whether iatrogenic hypoglycaemia plays a role in post-operative disturbances of cognition. Notzold et al, 2006 studied n=34 patients (n=14 diabetics, n=20 non-diabetics) undergoing CABG surgery. Pre-operatively tests examined the emotional NP state, stress-coping ability and quality of life. Emotional and NP tests were assessed daily from day 2 to 5 post-operatively. They found that in the diabetic group the post-operative NP outcomes were significantly longer (Stroop test P=0.02, the Abbreviated Mental test P=0.02 and the Trail Making test P=0.04) compared to non-diabetic patients[44].

Kadoi et al, 2005 studied 180 type II diabetic patients undergoing first-time CABG surgery to determine what type of type II diabetes related factors contribute to post-operative NP deficit. They matched the age, sex and educational level of these patients against 100 patients without diabetes as a control group. All patients underwent a battery of neurologic and neurological assessment the day before, 7 days and 6 months post-surgery. There was significant NP deficit at 7 days and 6 months after surgery related to insulin therapy, the presence of diabetic retinopathy and the level of haemoglobulin A 1c in the type II diabetic patients[45]. Therefore, in insulin-dependent diabetes mellitus it is unclear whether these patients are more at risk of NP deficits but there is evidence that the way in which serum glucose is managed on bypass can affect the NP outcome[46].

1.3.8. Peripheral vascular disease

Ancona et al in 2003 retrospectively analysed 9,916 patients from January 1999 to June 2002 who had undergone CABG surgery, out of which 280 patients had peri-operative stroke (2.1%). Univariate analysis identified peripheral vascular disease (PVD) as one of the determinants of neurological incidence[47]. Subsequently, the severity of PVD is also an independent risk factor of NP outcome (Phillips, Mate-Kole, 1997)[48].

Shaw et al, 1987 examined NP function in 312 patients before and after CABG surgery. Fifty patients with PVD undergoing surgery were used as a surgical control group and 20 non-surgical patients as a control group. Out of the 50 patients with PVD, 9 (18%) developed neurological complications resulting from trauma to lower limb sensory nerves. Two of the 50 developed primitive reflexes. Fifteen of 48 (31%) showed NP deficit[49].

1.3.9. Genetic

The association of apolipoprotein E (APOE) and NP dysfunction is well established in Alzheimer's disease. The gene coding for APOE occurs as three common alleles ε2, ε3 and ε4. APOE proteins are responsible for the repair of neuronal injuries that would make patients more susceptible for NP dysfunction in the post-operative period. Tardiff and co-workers' preliminary report of a genetic basis for NP deficit following CABG surgery in 65 patients in 1997, suggested that APOE genotype is related to cognitive decline[50]. This led to STOEd and co-workers in 2001 from London, England, re-examining Tardiff and colleagues' earlier work by increasing the sample size to 111 patients who were undergoing CABG. Their investigation and a recent study by Silbert et al suggested that the ε4 allele was not associated with NP deficit[51,233]. There is a need for a more wide-ranging investigation of genetic markers in an attempt to explain individual patient vulnerability in this context.

1.3.10. Educational level, socio-economic status and mood

Interestingly, higher numbers of years of formal education is found to protect patients from NP deficit[21]. It is still unclear whether higher education increases the cognitive reserve in an individual, thereby improving their test-taking capability or enhances neuronal homeostasis making them more resistant to neurological insult. Ho et al 2004 studied CABG surgery patients to identify patient-related risk factors, process of care and the occurrence of any intra-operative complications associated with NP deficit following surgery. Nine hundred and thirty-nine patients undergoing CABG surgery at 14 veterans' administration medical centres between 1992 and 1996 were enrolled into the Process, Structures and Outcomes of Care following surgery. They completed a short battery of cognitive tests at baseline (72 hours prior to surgery) and 6 months post-surgery. Interestingly, they showed that more years of education were associated with less NP deficit (p=0.001)[52].

A study albeit involving only 22 patients undergoing CABG surgery by Folks and colleagues suggests that lower socio-economic status may confer greater risk for post-operative NP morbidity[53].

It is also quite interesting to know whether pre-existing NP problems such as depression and altered mood status have any influence on the post-operative outcome following CABG surgery. McKhann and colleagues in 1997 assessed 124 patients using the Centre for Epidemiological Study OF Depression (CES-D) scale along with a series of NP tests. Patients with a CES-D score above 16 were defined as depressed. Only 12 (13%) of patients not depressed before surgery were depressed 1 month afterwards, whereas 18 (53%) of those who were depressed before surgery were depressed at one month (p=0.001). At the one-year follow-up, 8 (9%) patients not depressed before surgery and 16 (47%) patients depressed prior to surgery were depressed (p=0.001)[54].

In 2001, Millar and colleagues studied 81 out of 120 patients who underwent CABG surgery. Their patients performed the Stroop Neuropsychological Screening Test and other psychometric assessment prior and 6 days and 6 months post-surgery. The presence of pre-surgery depression was found to be a significant predictor of post-operative state at 6 days follow-up (p<0.001). At 6 months there was no late onset impairment: No patient was impaired without having previous impairment[55].

1.4. Surgery/Procedure-related variables

1.4.1. Cardiopulmonary bypass

Cardiac surgery involving CPB has undergone many changes since its introduction starting with the bubble to the membrane oxygenator CPB machine. Padayachee et al in 1987 studied 27 patients who underwent CPB surgery (bubble n=17, membrane n=10). They showed membrane oxygenators to produce fewer ME as detected by TCD when compared to a bubble oxygenator[56]. Subsequently, the study by Smith et al 1990 compared these two oxygenators to detect any relationship between cerebral microembolisation and NP outcome. They found membrane oxygenators to cause less NP deficits[57]. A randomized controlled trial of 103 patients by Scott et al in 2002 found no difference in early (5 day) NP outcome with roller or centrifugal bypass pumps[58].

1.4.2. Duration of Cardiopulmonary bypass

Several studies over the years have shown that NP deficits were found to increase with a prolonged duration following CPB[59,60,61] while some did not confirm this effect (Hammeke 1988)[62]. Brown et al described a post mortem examination of brain specimens obtained from 36 patients who died within 3 weeks after CPB[63]. Specimens were embedded in celloidin and stained with endogenous alkaline phoshatase. This outlined the arterioles and capillaries. In such preparations emboli could be seen as swellings in these vessels. Cerebral ME were then counted as small, medium or large in order to estimate the overall emboli load. They found thousands of ME in these specimens soon after CPB. They concluded that the longer duration of the bypass was associated with a significantly increased embolic load (P=0.0026). An interesting finding was that as time increased following the bypass, the percentage of large and medium emboli decreased (P=0.0034), thereby suggesting that emboli break into smaller globules with time as they pass through the capillary network.

It is also important to note that numerous factors and circumstances may contribute to prolong the duration of CPB time. Technical problems or complications during surgery along with difficulty in weaning the patient off CPB are the main causes of prolonged bypass. With an ever-increasing group of high-risk patients undergoing CABG surgery, from the foregoing discussion it is clear that all these factors may contribute to a higher risk of neurological and NP outcomes.

1.4.3. Inflammatory response to CPB

CPB is associated with an interaction between blood and foreign surfaces producing a "whole body inflammatory response". This produces a systemic inflammatory reaction (SIR) that can often lead to dysfunction of major organs especially the renal and pulmonary system. Leucocytes in particular neurophils, once activated are thought to interact with blood components and the vascular endothelium to produce tissue injury and possibly ME. These inflammatory processes have been suspected to cause NP deficits[64,65,235,236]. However, their effects on the cerebral system are less well understood. Despite this, there have been conflicting findings regarding the impact of the inflammatory process on post-operative NP outcome.

Increased blood concentrations of the glial protein S100β have been measured after operations using CPB and in some studies have appeared to be associated with neurological complications. However, this protein is not only restricted to brain tissue, but is also found in peripheral nerves, extracts of fat, bone marrow and organs of mesenchymal origin[66,67] . The blood levels of inflammatory mediators were found to be significantly raised in shed mediastinal blood obtained by cardiotomy suction during and after surgery[68]. The half life of S100β is approximately 25 minutes and therefore its presence in the circulation 24 hours following cardiac surgery has been used as a useful marker of late mortality by Johnnson et al[69]. Rises in S100β have also been seen in non-cardiac surgical patients following spinal surgery[70].

A study using S100β by Georgiadis et al, in 2000 assessed 190 consecutive patients undergoing elective cardiac operations for CABG surgery (n=147), valve surgery (n=29), or both (n=14). This and the 1999 study of Kilminster et al involving 130 cardiac patients having pre and post-operative neurological assessment showed a correlation between increased levels of S100β early after the operation and neurological complications[71,72]. Several factors have been implicated in the initiation of an inflammatory response. The factors include exposure of blood to foreign surfaces, ischaemic-reperfusion of organs, surgical manipulations, non-pulsatile flow and endotoxin release. These in turn activate the complement, coagulation, fibrinolysis and kallikrein-kinin pathways leading to leucocyte activation.

Because of the complement mediated brain cell injuries that occur following the exposure of blood to the foreign surfaces of the cardiopulmonary bypass circuit, Baufreton et al in 2004 randomly assigned 30 patients undergoing coronary surgery to either a standard non-coated or heparin-coated (to decrease possible complement activation) bypass circuit in order to evaluate the role of complement activation on cellular cerebral injury. NP assessment tests were conducted 2 week prior and at the time of discharge while sC5b-9 levels tested complement activation. The sC5b-9 levels were found to be significantly higher in the non-coated group at the end of CPB (p=0.005). Glial injury was measured using s100β levels at different times before, during and after CPB. At the end of CPB, the levels were significantly higher in the non-coated group than in the coated group (p=0.008). Higher levels were still seen in the non-coated group 4 hours after initiation of CPB (p=0.02). When they compared the correlation between inflammation, atheroma and cerebral injury, the incidence of aortic atherosclerosis did not differ significantly between the two groups. However, s100β levels at the end of the CPB were found to be higher in the patients who had severe ascending aortic atheroma when compared to those with intimal thickening (p=0.018)[73].

Westaby et al, 2001 in a prospective study involving 100 first-time CABG surgery patients sought evidence of any relationship between NP deficit and systemic inflammatory response following CPB. Inflammatory markers (complement release products C4a, terminal complement complex C5b-9, Interleukin-6) and markers of coagulation and fibrinolysis (platelet degranulation-β- thromboglobulin, thromboxane B2, prothrombin activation-F1+2, D-dimer) were analysed at several time points during and after the operation. A battery of NP tests was used a day prior and at 5 days and 3 months post-surgery. Out of the 95 patients who satisfactorily completed the pre-operative assessment, only 79 patients completed the 5-day post-operative assessment. Two patients were excluded because of stroke and the remaining 14 declined the time consuming examination at that time. However, at the 3-month post-operative period, 89 patients were able to complete all the tests. Their study was unable to detect any significant correlations between the inflammatory markers and NP outcomes at 5 day and 3 months post-surgery[74].

In summary, due to the lack of a reliable and specific marker of brain inflammation that could be used after CPB, the role of systemic inflammatory response in neurological injury following cardiac surgery is still open for debate. Various strategies have been used to reduce inflammatory phenomena in patients undergoing CPB. Blood collected from the surgical field is filtered and washed prior to reinfusion. Although widely accepted in cardiothoracic literature, this strategy has never been formally evaluated in any large-scale study. The emergence and expanding performance of cardiac surgical procedures without the use of CPB has given us an excellent tool to investigate the relative importance of CPB as a cause of systemic inflammation.

1.4.4. Perfusion: Pressure, flow, arterial filter and pulsation

Global hypoperfusion of the brain has been implicated as an important factor in the aetiology of NP deficits during cardiac surgery[75]. In recent years there has been much debate regarding the perfusion pressure needed during CPB to maintain adequate cerebral blood flow. Mean arterial pressure (MAP) is the major factor affecting cerebral perfusion pressure (CPP). Cerebral blood flow (CBF) is maintained at a relatively constant level by auto regulation over a wide range of perfusion pressure (50-150mmHg). Perfusion pressure below 50mmHg is associated with a fall in CBF, subjecting an individual to potential cerebral ischaemia. The parieto-occipital cortex, which lies at the boundary supplied by all three cerebral arteries is the most vulnerable watershed areas[76].

There is, however, some evidence that hypoperfusion can be a significant contributory factor in cardiac surgery relating to ischaemic cerebral injury. Tufo et al who studied 100 patients undergoing CABG in 1970 found that the incidence of post-operative neurological insults was higher (78 vs 27%) in those with a mean perfusion pressure of 40mmHg compared to 60mmHg[72]. But in a later study, Gold et al (1995) investigated the use of higher pressures by prospectively studying cardiac and neurological outcome in 248 patients undergoing elective CABG in two groups with lower (50-60 mmHg) or higher (80-100mmHg) pressures. Six months after surgery the overall incidence of cardiac and cerebral complications was significantly lower in the higher pressure group (4.8% Vs 12.9%,p=0.026), as was the stroke rate (2.4% Vs 7.2%) but their study failed to show any NP differences between the groups[78], while some showed improvement with higher pressure[228].

However, Caplan et al suggested that cerebral blood flow may have a significant effect on NP and neurological outcomes via effects on ME. This study hypothesised that the effect of emboli was worse when the perfusion pressure to the brain was less because there is less "washout" of emboli. However, the study failed to show any direct evidence to support this[79]. Theoretically, a higher cerebral flow rather than pressure could deliver more microemboli to the brain.

Although various arterial filters have been used, they are still not being used universally. At present they are popular, especially in the United States of America, due to their ability to remove microemboli and also larger air emboli in the event of a perfusion accident[80]. A recent study by Whitaker et al using leucocyte depleting arterial filter during CABG showed that by reducing the number of ME release, the overall NP outcome was better[81].

With regard to pulsatile vs non-pulsatile flow, various studies have shown different patterns to perfusion and NP outcomes. Murkin and colleagues in a prospective double-blinded randomised study of 316 patients undergoing CABG in 1995 were not able to show any changes[82].

1.4.5. Temperature

The main question between temperature management during CPB and subsequent NP outcome has been debated along temperature at which CPB is conducted and the rate at which rewarming is achieved. Hypothermia has been used as a cardioprotective and neuroprotective strategy throughout the development of cardiac surgery. The following studies have investigated the effects of normothermic compared to hypothermic bypass on cerebral and NP outcomes with conflicting results.

Grigore and colleagues[83] 2001 at the Duke Heart Cente investigated a prospective randomized trial of normothermic vs hypothermic CPB on NP outcome after CABG. Out of 300 patients, 149 were in the normothermic group (35.5-36.5°C) and 151 in the hypothermic group (28-30°C). In the final analysis of the 227 patients who took part in the 6-week NP follow-up, hypothermic CPB did not provide any additional protection to the brain when compared to normothermic CPB.

Rewarming after hypothermia is theoretically a potential cause for cerebral and NP dysfunction due to enhanced cerebral metabolism. Grigore et al, in a recent randomized study using slow or more rapid rewarming of patients from hypothermia found that the NP outcomes were better among the slow rewarming group at 6 weeks post-surgery[84]. It has also been suggested that rapid rewarming may produce ME from the anaesthetic gases. Nathan et al examined the effects of two different rewarming methods at the end of CPB. In their randomised study all patients were cooled to 32˚C during CPB and then rewarmed to either 34˚C or 37˚C with no further rewarming. They used a battery of 11 NP tests and found incidences of 62% and 48% deficit at 1 week post-surgery in patients randomly allocated to normothermia or hypothermia at the time of rewarming on CPB, even though their findings suggested that the 34˚C group had a less NP deficit at 1 week and 3 months post-operatively. At 3 months, the difference was seen in only 1 of the 11 tests, suggesting that the difference between the groups at 1 week was a temporary effect, which disappeared by three months[85]. The same investigators in their 5-year follow-up of the study in 2007 reported that patients who had greater neuro cognitive decline at 1 week after surgery showed poorer performance 5 years later. They also found that the magnitude of cognitive decline over 5 years was modest and the incidence of deficits was not different between temperature groups. Finally, only a few patients in the hypothermic group had deficits that persisted over the 5 years, with no statistical significance (RR=0.64, P=. 16). They concluded that even though there was evidence of a neuroprotective effect of mild hypothermia early after surgery in the original cohort, the results after 5 years were inconclusive, warranting further studies[86].

In summary, even though hypothermia is neuroprotective it may be the very process of rewarming to normothermia and above that is harmful. The effects of the rate and extent of rewarming on cerebral outcome have not been studied but their potential effect must be remembered if hypothermia is used.

1.4.6. Acid-base management

As temperature decreases, the solubility of carbon dioxide (CO2) in blood increases. Thus during hypothermic CPB as the temperature drops, the partial pressure of CO2 (pCO2) decreases. Arterial blood gases when analysed during hypothermia would give a picture of respiratory alkalosis (decreased PaCO2 and increased pH). Acid-base can be managed by two methods ‘pH-stat’ involving the addition of CO2 to normalise the PaCO2 and maintain a pH of 7.40 or ‘alpha-stat’ involving blood gases being measured at 37°C regardless of body temperature.

There is evidence that alpha-stat management leads to a better cerebral and NP outcome.

Bashein and colleagues in 1990 reported that there were no influences using pH stat or alpha stat management[87]. But Stephan and colleagues in a randomized study involving 65 patients showed a higher incidence of NP deficits using pH-stat management[88]. This was also supported by Murkin et al in a randomized study involving 316 patients where alpha-stat managed patients had less NP deficits especially in patients who were subjected to more than 90 minutes of CPB[82]. Other studies have also reported similar findings[89,90].

Patel et al in 1996 randomized 70 patients to either pH-stat or alpha-stat control and both the groups were cooled to 28˚C. Their study showed a NP deficit in the pH-stat group at 6 weeks post-surgery. They also detected an increase in cerebral blood flow velocity along with hyperaemia especially in the pH-stat group. Their study suggests that since pH stat management disturbs the normal auto regulatory mechanism of cerebral blood flow there is an increased association of diffuse cerebral insult[89]. It has been suggested that an increase in flow leads to an increase in the number of ME delivered to the brain.This has been suggested from animal model studies that a reduction in temperature or an increase in PaCO2 levels can lead to increased cerebral blood flow along with an increased number of ME being delivered to the brain[91]. But Patel in his study did not measure ME[89].

1.5. Atheromatous disease in the ascending aorta

From previous studies of CABG surgery patients, it is apparent that over 50% of patients who present for cardiac surgery have evidence of either extracranial or intracranial atherosclerotic disease[92]. With the increase in the mean age of patients undergoing coronary artery surgery, the incidence of aortic atheromatous disease has also gone up steadily. Some studies suggest that CPB and manipulation of the aorta are the two most likely sources of poor NP outcome during conventional CABG[93] and because of this, there is a close relationship with any cerebral embolic event occurring during surgery[94,95,96,97].

A later chapter looking into the detection of atheromatous disease in the ascending aota using various screening techniques like Digital palpation (DP), Transoesophageal echocardiography (TOE) and Epiaortic ultrasonography (EAU) will discuss its close relation to ME and its impact on NP outcome.

1.6. Microembolism

Cardiopulmonary bypass increases the permeability of the blood –brain barrier[230] and generates microemboli (ME), which may effect the NP outcome.A number of investigators maintain that the atheroma of patients is the most significant of the ME sources and that atheromatous ME are detrimental to the NP outcome[98, 99,100]. But when all studies are considered it seems that ME are multifactorial with many sources. The fact that ME are detectable in children having surgery to correct congenital cardiac defects suggests that non-atheromatous sources are also important in the production of ME[101].

We will discuss in detail in a later chapter how ME could be identified "live" using TCD during CABG surgery and investigate whether there is a co-relation to the NP outcome.

1.7. Myocardial protection techniques

Since the mid 1970's Cardioplegic arrest (CA) has been the most widely practised technique for myocardial protection. Nevertheless, intermittent cross-clamp fibrillation (ICCF) has continued to be preferred by a minority of surgeons in both high and low-risk patients[102]. Various studies have shown ICCF to be a safe or safer strategy than CA for the heart through preconditioning[10,103,104,105,106,107]. Exponents for ICCF claim that the technique is simpler, allowing the myocardium to be reperfused during the procedure, and has the potential to result in shorter ischaemic and CPB) times[103].

However, ICCF is known to be associated with more handling and repeated clamping of the aorta. It has been argued that in the presence of atheromatous disease, this manipulation may cause plaque adhering to the aortic wall to crack or rupture releasing debris (microemboli) into the systemic circulation and that a proportion of these ME could eventually find their way into the cerebral circulation[108,109]. The surgical manoeuvres identified as being most likely to cause this disruption are aortic cannulation/decannulation, cross-clamp application/removal and construction of proximal anastomises[11,99].

Despite various studies comparing the effectiveness of the myocardial protection benefits, unfortunately there is only one small study that has compared the post-operative generation of ME and NP outcomes in patients undergoing either ICCF or CA during CABG surgery[10].

Subsequent chapters will study in detail some of the variables to see if there is a possible association between NP outcome and ME generation during CPB using ICCF or CA as the myocardial protection techniques.

Chapter 2

Role of atheromatous disease in the ascending aorta in neuropsychological outcome during cardiopulmonary bypass

2. Role of atheromatous disease in the ascending aorta in neuropsychological outcome during cardiopulmonary bypass

2.1. Introduction

The natural history of atheromatous disease is a slowly progressive systemic inflammatory process of the arterial system with plaque formation associated with intimal thickening that takes place over several decades starting from childhood. The usual morphological features include cellular proliferation, lipid accumulation, inflammation, necrosis, fibrosis and calcification. Ulceration of these plaques may result in embolisation, which can lead to NP deficits, stroke and death. These findings have been validated following clinical trials and post-mortem findings[109,110].

Recent investigators have been able to demonstrate that the incidences of cerebral (stroke,TIA and NP deficits) complications were significantly higher in patients who had been shown to have a higher atherosclerotic burden in the brain, carotid arteries and the ascending aorta[111].

CABG involves manipulation of the ascending aorta by arterial cannulation, cross-clamping and side-clamping, all of which can increase the risk of embolisation of atherosclerotic material to the brain. This along with other co-factors such as advancing age of patients have all been implicated in causing NP complications following CABG surgery due to the presence of atherosclerotic lesions in the ascending aorta.

This chapter will review the literature to further elucidate the various screening techniques available to detect atheroma and examine whether there is any relationship between atherosclerosis of the ascending aorta and NP outcome after CABG surgery due to the handling of the ascending aorta during surgery using the conventional CPB machine.

2.2. Incidence with associated co-morbid factors

The presence of atherosclerosis in the ascending aorta is an important risk factor for cerebral embolisation leading to stroke and associated NP problems during CABG surgery. Although an association between atherosclerosis of the aorta and peripheral embolism has been speculated over the years, the importance of the ascending aorta as a source of cerebral and vascular emboli has only recently been established. Blauth et al provided evidence for the role of aortic atheroemboli. Their study of 221 post-mortems established that atheroemboli were more common after coronary revascularisation than after valvular procedures (p=0.008). Peripheral vascular disease and ascending aortic atherosclerosis were significant independent risk factors for atheroemboli. Atheroembolic events occurred in 46 of 123 patients (37.4%) with severe disease of the ascending aorta but in only 2 of 98 patients (2%) without significant ascending aortic disease ($p < 0.0001$). Forty-six of 48 patients (95.8%) who had evidence of atheroemboli had severe atherosclerosis of the ascending aorta. Their study showed a direct correlation between age, severe atherosclerosis of the ascending aorta, and atheroemboli[112].

Davila-Roman et al 1991 relied on EAU to detect atherosclerosis in high-risk patients. An analysis of pre-operative variables revealed that age and diabetes were the only significant independent predictors of severe atherosclerosis identified by EAUof the ascending aorta[113].

Davila-Roman et al 1999 in a prospective study involving a cohort of 1,957 consecutive patients evaluated their ascending aortas with EAU at the time of cardiac surgery starting from January 1990 to May[114]. The cardiac surgical procedures performed included: CABG surgery in 1,472 (75.2%), valve repair or replacement in 224 (11.5%) and combined valve and CABG surgery in 261 (13.3%). Of the 1,957 patients who underwent follow-up 1,147 (58.6%) had a normal ascending aorta, 461 (23.5%) mild atherosclerosis, 250 (12.8 %) moderate atherosclerosis and 99 (5.1%) severe atherosclerosis of the ascending aorta. A total of 491 events occurred in 472 patients (Ccerebral events 92, all-cause mortality 399). They showed a statistically significant association between hypertension ($p=0.009$), atherosclerosis of the ascending aorta ($p=0.011$) and diabetes mellitus ($p=0.015$). The independent predictors of mortality were advanced age ($p<0.0001$), left ventricular dysfunction ($p<0.0001$), ascending aorta atherosclerosis ($p<0.0001$), hypertension ($p=0.0001$) and diabetes mellitus ($p=0.0002$). There was >1.5-fold increase in the incidence of both cerebral events and mortality as the severity of atherosclerosis increased from normal-mild to moderate and a greater than 3-fold increase in the incidence of both as the severity of atherosclerosis increased from normal-mild to severe. Their prospective study was the first to show that atherosclerosis of the ascending aorta is an independent predictor of long-term mortality. They were also able to show that in patients with severe atherosclerosis of the ascending aorta there was a three-fold increase in cerebral and all-cause mortality rate when compared with patients with a normal ascending aorta.

The Schachner et al[115] study examined 500 patients undergoing coronary surgery between 1998 and 2003 to determine factors that would predict the presence of atherosclerotic wall thickness in the ascending aorta. Maximum ascending aortic wall thickness significantly correlated with age ($p<0.001$), pre-operative creatine level ($p=0.004$), European system for cardiac operative risk evaluation (EuroScore, $p< 0.001$), and maximum descending aortic wall thickness ($p<0.001$).

Van der Linden et al[116] prospectively studied 921 consecutive patients undergoing elective cardiac surgery to evaluate the risk of calcified atheroma in the ascending aorta and the extent and topography of the disease in the development of stroke after cardiac surgery. The presence of calcification, location of atheroma, extent of the disease and clinical variables such as stroke were recorded. The ascending arch and descending aorta was screened using DP, TOE and EAU. A total of 26.2% of the patients had atheroma in the ascending aorta. Logistic regression showed that atherosclerotic disease in the ascending aorta was the most predictive factor for post-operative stroke. The incidence of stroke was 1.8% in patients without atherosclerotic disease and 8.7% ($p<0.0001$) in patients with the disease in the ascending aorta. Diabetes mellitus was also a predictive factor ($p=0.04$). An interesting finding of this study was that the middle-lateral segment was an independent predictive factor for post-operative stroke, with a relative risk of 26% ($p=0.04$).

A direct correlation between age and ascending aortic atherosclerosis was also found. Approximately 20% of patients 50 years of age or over undergoing cardiac surgery have atherosclerotic disease in the ascending aorta[115].

Kapetanakis et al in a risk-adjusted study involving 7,272 patients undergoing CABG surgery showed that the incidence of post-operative cerebral injury increases with aortic manipulation[108]. Therefore, detection of atheroma in the ascending aorta prior to manipulation during coronary artery surgery is considered to reduce the overall incidence of neurological injury and NP dysfunction, especially in elderly patients[115,117].

Also several other investigators such as Blauth 1992[112], Roach 1996[64], and Hogue 1999[118] have all suggested a correlation between the presence of atherosclerosis in the ascending aorta and post-operative neurological events. Therefore, it seems evident that atherosclerosis of the ascending aorta must be identified during the intra-operative period to minimize the risk of a cerebral atheroembolic event[119].

Theoretically, aortic cannulation, clamping, manipulation and de-cannulation could all lead to the release of atheromatous material from the ascending aorta and cause cerebral vascular accidents (CVAs). Identifying the sites and severity of atheroma in the ascending aorta intra-operatively is now postulated as an important prelude to minimize the incidence of adverse cerebral events in the intra-operative period.

2.3. Different screening techniques

An ordinary chest X-ray for the pre-operative identification of atherosclerosis of the ascending aorta visualizes only the large calcified areas and thus underestimates the frequency of atherosclerosis[120].

In this chapter we will investigate three techniques that are commonly used intra-operatively to assess atheroma in the ascending aorta:

- Digital palpation (DP)
- Transoesophageal echocardiography (TOE)
- Epiaortic ultrasonography (EAU)

We shall also investigate which imaging technique might be the so-called “Gold Standard” in identifying atheroma.

2.3.1. Digital palpation

Digital palpation (DP) has historically been the primary method of detecting atherosclerosis in the ascending aorta during surgery. It is a simple method commonly used by surgeons to directly assess the aorta by feeling for any abnormality and grading them according to the consistency felt. DP has also been very widely studied but with evenly unimpressive results. Ohteki et al 1990[121] in a prospective study assessed 100 patients with coronary disease using DP and compared the results against transoesophageal and computed tomography. They found that DP detected only 25% of the atherosclerotic plaques that were detected echocardiographically, while both DP and computed tomography undervalue the frequency of detection of atheroma compared to EAU. Another study by Sylviris et al 1997[122] (n=100 patients undergoing coronary or valve surgery) found that DP underestimated the severity of atheroma in the ascending aorta when compared against ultrasound imaging techniques in up to 69% of the patients.

2.3.2. Transoesophageal echocardiography

The American Society of Echocardiography (ASE) established the Council for Intra-operative Echocardiography in 1993 and 1997; the council board created a set of guidelines[123].

Although the use of Trasnoesophageal echocardiography (TOE) to detect atheroma has been standard practice in CABG surgery, there are problems in visualizing the mid and distal portions of the ascending aorta with this technique as the trachea lies between the oesophagus and the distal ascending and proximal aortic arch. These regions are difficult to image and cannot be assessed reliably. This is an important segment of the ascending aorta since aortic cannulation and application of the aortic cross-clamp is usually placed in the distal segment of the ascending aorta. Therefore, Konstadt and co-workers[124] in 1994 used TOE to see how far it can be used to image the ascending aorta. They examined 27 patients undergoing cardiac surgery. The ascending aorta was directly measured independently by the surgeon starting from the annulus to the origin of the innominate artery [length of 8.9 +/- 1.3cm (mean +/- SD)] and to the level of the aortic cannulation site. These measurements were compared against TOE (7.4 +/- 1.1cm) measurements. Both TOE and EAU were also used to assess the aorta for any atheroma. The range of the difference between the two measurements was 0.2-4.5cm. The aortic cannula was seen only in 1 of 27 patients and severe atherosclerotic plaques (>3mm thick) not seen on TOE were detected in 5 patients with EAU. As much as 42% (4.5cm of 10.7cm) of the length of the ascending aorta was not visualized and potentially embolic plaques were not imaged by TOE. These findings suggest that TOE may have limited use in the pre-cannulation assessment of the aorta for plaque and the detection of distal ascending aortic pathology.

The same author in 1995[125] examined the entire thoracic aorta to predict the presence of plaque in the ascending aorta in n=81 patients. Using EAU as the "gold standard", the sensitivity, specificity, positive predictive value, and negative predictive value of TOE for detecting ascending aortic atherosclerosis were calculated. Using epiaortic ultrasound four (17%) of the 81 patients had significant atherosclerotic disease of the ascending aorta. The sensitivity of TOE was 100%, the specificity 60%, the positive predictive value 34% and the negative predictive value 100%. These data show that if the complete biplane TOE examination is negative for plaque then it is highly unlikely that there is significant plaque in the ascending aorta. If the TOE examination is positive for plaque then there is a 34% chance that there is significant disease of the ascending aorta and an EAU should be considered. Other studies by Marshall 1989[126] and Davila-Roman 1996[127] had also shown that TOE significantly underestimates the severity of ascending aortic atherosclerosis, particularly in the distal ascending aorta.

This has led investigators to use EAU that is able to directly image the proximal, mid and distal portions of the ascending aorta[127,128,129].

2.3.3. Epiaortic ultrasonography

Intra-operative assessment using epiaortic ultrasonography (EAU) is a technique that was introduced by Marshall et al[126] for patients undergoing cardiac surgery. Using EAU, atherosclerosis was diagnosed by this method in 58% of a selected series of patients wherein the surgical technique had to be changed in 24% of patients overall because of its findings. Several investigators have confirmed EAU to be superior to TOE and DP for assessing the ascending aorta (Konstadt 1994[124], Davila-Roman 1996[127], Syliviris 1997[122], Roysce 1998[130], Wilson 2000[109], and Bolotin 2005[128]).

Most often atherosclerotic disease can be identified in 20-25% of the patients, especially in the distal segments of the ascending aorta using EAU (van der Linden 2001[118], Davila-Roman 1994[113] and Marshall 1989[126]).

Although the details of the ascending aorta can easily be obtained there are still doubts whether topographic pathology can have an impact on the incidence of post-operative neurological deficits. There is one study by van der Linden et al[116] which showed that if the ascending aorta was divided into 12 segments i.e. three transverse and four longitudinal, then the distal anterior segment tends to be more affected than any other segment.

However, EAU has been claimed to reduce the incidence of intra-operative stroke by leading to changes in surgical techniques by detecting diseased segments of aorta as shown by Wareing et all in1992[119].

2.4. Location and grading of atheroma

Understanding the distribution pattern of the atheroma along the ascending aorta is important so that by identifying the exact location of the atheroma, the surgeon can determine what portion of the aorta should be avoided during surgical procedure.

Tobler and Edwards[131] studied the frequency and location of atherosclerotic plaques in the ascending aorta. Ninety-seven adult specimens with coronary disease were examined. The right side of the ascending aorta was more commonly involved than the left. The sites least commonly involved were the right posterior, upper-right anterior and lower posterior locations. In specimens with plaques at the orifice of the innominate artery, nearly 80% had plaques in the ascending aorta and 73% of specimens with plaques at the orifice of the left subclavian artery had plaques in the ascending aorta.

Atherosclerosis of the aorta has been graded by several ways using ultrasonography of intimal thickening (Wareing et al 1993[119], Ribakov et al 1993[132] and N. Trehan et al 2000[133]) (Table2. 1).

Table 2.1

Grading of aortic atheroma (Adopted by Trehan et al)

Grade 1	Plaque less than 5mm into the aortic lumen
Grade 2	Plaque more than 5mm into the aortic lumen
Grade 3	Plaque with a mobile element

Initial case studies in the US classified intimal thickening of 5mm and above as significant atheroma [134] (Table 2.2).

Table 2.2

Adopted by Tunick et al

<1mm	OR=1.0
1-3.9mm	OR=3.9
>4mm	OR=13.8

Intimal thickness in mm, OR= Odds ratio

However, subsequent studies by the French Aortic Plaque in Stroke (FAPS) group by Amarenco et al[129] in 1994 evaluated 500 patients over the age of 60 years. They concluded that the increase in odds ratio (OR) for an embolic event was as follows: The intimal thickness<1mm OR=1.0 (no increased risk); for 1 to 3.9mm OR=3.9; and for plaques >4mm OR=13.8 (Table2.2). It must be noted that they qualified that this risk may have also been associated with the presence of carotid stenoses.

Table 2.3

The French Aortic Plaque in Stroke (FAPS) group

< 1mm	No risk
1 - 1.9mm	Increases cerebrovascular events
2 - 2.9mm	
3 – 3.9mm	
> 4mm	Marked increase in cerebrovascular events

Intimal thickness in mm

In a subsequent 1996 study the French Study of Aortic Plaque in Stroke (FAPS)[135] group evaluated 331 patients and although they confirmed a markedly increased risk with plaques greater than 4mm, there was a significant increase in cerebrovascular events with plaques between 1 and 3.9mm. Several other studies have also shown that the presence of severe atheroma is associated with higher incidence of cerebral injury[115,117,136].

Davila-Roman et al[137] divided the ascending aorta into three equal segments between the aortic annulus to the innominate artery. They graded atheroma as mild atherosclerosis if intimal thickening (<3mm) involved only 1 segment of the ascending aorta, as moderate if intimal thickening (>3mm) involved 1 or 2 segments and severe if intimal thickening

(>3mm) involved all three segments or occurred circumferentially around the aorta (Table2. 4).

Table 2.4

Grading of atheroma Davila-Roman et al

Score	**Description**	**Definition**
0	No atheroma	No atheroma
1	Mild atherosclerosis	Intimal thickening <3mm
2	Moderate atherosclerosis	Intimal thickening >3mm
3	Severe atherosclerosis	Circumferential thickening>3mm or pedunculated Plaque

Intimal thickness in mm

Grading was also important in predicting the incidence of intra-operative stroke in a study by Mizuno & colleagues. This study of 315 consecutive patients undergoing CABG surgery found that when the aortic arch intima was >5mm, patients were at significantly greater risk of intra-operative stroke[138].

2.5. Gold standard imaging technique

While it is inevitable that any imaging technique will have both false positives and negatives, EAU currently seems to offer the best sensitivity and specificity of all the intra-operative techniques. Although EAU has become the gold standard for detecting atherosclerotic changes in the ascending aorta it can only be used to detect atheroma during the intra-operative period. If the findings do not reflect the anticipated diagnosis then a decision regarding technique has to be made during surgery. However, it would be better if such decisions could be made pre-operatively. Hence to support the “gold standard” assumption one should also determine whether other imaging techniques such as CT scan could evaluate severe atherosclerosis in the ascending aorta as effectively as intra-operative EAU. Bergman et al screened 20 consecutive patients for atherosclerotic disease in the ascending aorta undergoing elective coronary surgery and compared pre-operative CT with intra-operative EAU findings. AS EAU detected atherosclerosis in a significantly higher proportion of patients than CT, they concluded that CT scanning was inferior to today’s gold standard method of EAU in detecting the extent and location of atheroma in the ascending aorta[139]. Finally, as indicated by Summers et al other non-invasive diagnostic techniques including MRI might also be of great value in the pre-operative evaluation of severe atherosclerosis in the ascending aorta[140].

2.5. Discussion

In contrast to TOE and EAU, DP fails to identify significant plaques in the ascending aorta in 50-60% of the cases as shown by van der Linden 2001[116] and Marshall 1989[126]. A second limitation is the lack of a uniform classification system for grading atherosclerosis of the ascending aorta as various investigators have used different cut-off values to define atheromatous lesions in the wall as pathologic: 0.5mm (van der Linden 2001[116]), 1.0mm (Amarenco 1994 [129] and Sylivris 1997 [122]) and 3.0mm (Hangler 2003[141], Lev-Ran 2005[142], Davila-Roman 1999[100] , and Konstadt 1995[111]). Moreover, the number of grades used to classify intimal thickening has varied, being expressed in two categories mild or severe[122,129], three catogories mild, moderate or severe[114,136,141] or even in four catogories mild, moderate, severe I and severe II[143].

2.6. Summary

A correlation between the degree of coronary artery disease and the extent of atherosclerosis of the ascending aorta is becoming a common risk factor for stroke and NP deficit following coronary surgery. The level of risk depends on the presence, location and grade of the disease especially when the ascending aorta is surgically manipulated. Several studies discussed in this chapter suggest that intra-operative EAU use should be routine, so that surgical manipulation could be reduced or when possible avoided in patients with atherosclerosis of the ascending aorta. With this in mind we have used EAU for screening the ascending aorta along with the traditionally used TOE and DP method in this thesis, comparing ICCF with CA so as to minimize the possible incidence of and embolic event during CABG surgery.

Since elderly patients with more advanced coronary artery disease are likely to have vascular disease of the cerebral circulation and might, therefore, be more susceptible to microembolic (ME) injury than the younger patients during coronary artery bypass grafting surgery. The next chapter we will look into this in detail.

Chapter 3

Microemboli

3. Microemboli

3.1. Introduction

Microemboli (ME) are emboli that are less than 200μm in diameter[144]. The precise composition of these ME is not clear. They may be gaseous, particulate or lipid with further subdivisions into natural or inert material. Both gaseous and particulate materials cause obstruction of distal end-arterial flow in cerebral arteries, resulting in end-organ failure. In addition ME are thought to cause secondary to local inflammatory responses[145].

The generation of ME during CABG surgery has been implicated as a possible aetiological cause of cerebral injury. This section will describe their composition; explain the various means by which they can be detected especially using TCD and review literature to find any possible link or evidence that might support their involvement in causing NP dysfunction during CABG surgery.

3.2. Gaseous Microemboli

Air is one of several sources of gaseous ME that could possibly cause central nervous system injury. Anaesthetic gases are more commonly implicated in the production of ME[130]. Gaseous ME can also occur due to the CPB circuit or the surgical techniques used. There is evidence that cannulation of the aorta and right atrium can entrap air. Air has been shown to be entering the right atrium via the venous cannula if the purse string holding it is inadequate, especially since the right atrium is sub-atmospheric in pressure. Air or oxygen can enter via the bypass circuit. Bubble oxygenators that were used previously generated more ME than the present membrane oxygenator thereby reducing the incidence of NP outcome with this newer technique[146].

It has been shown that during open heart surgery air commonly enters the left side of the heart and despite the best techniques used for de-airing, there will still be some “air bubbles” left behind[147]. Oka et al[148] used TOE for the definition of the incidence and monitoring of the removal of retained air. They showed retained air in 2 of 18 (11%) of patients having CABG compared to 12 of 15 (79%) who underwent valve surgery. Trace or moderate amounts of air were still seen in the left atrium or aorta 1 to 5 minutes post-CPB.

During the rewarming phase of the CPB, the partial pressure of gases would increase and tend to force them out of the solution and, therefore, there is an increased chance of bubbles being generated at this time. Rapid rewarming could thus have a damaging effect on NP function because of this but unfortunately there are no studies that examine the rate of rewarming and ME production.

3.3. Particulate Microemboli

The sources of particulate ME are numerous. They could be thrombin, fibrin, platelets, leucocytes, fat globules, atheroma, calcium and even denatured proteins. Studies have shown an increase in the number of ME during aortic cannulation and this is thought to be due to atheromatous or calcific debris rather than air.

Several investigators have shown atheroma to be the most significant of ME sources causing an unfavourable NP outcome[99,149]. However, when these studies are analysed it seems that ME are heterogeneous in origin with many sources. ME generation in children undergoing congenital cardiac correction suggests that non-atheromatous sources are also involved in their production[99,102,149].

Liu et al used a Coulter counter (an electronic particle-size analyser) and an electron microscope to quantify particulate ME during CPB in-vitro. Particules between 15 and 80μm in diameter were detected and viewed directly[150]. They found that the three sources of ME were transfused blood, the cardiotomy reservoir and the bubble oxygenator. Liu and co-workers showed that in the first hour of bypass there was a linear correlation between time of perfusion and blood destruction. The number of ME detected, steadily increased during the first hour and then ceased to change after that. Particulate ME may be generated by damaged blood elements and their subsequent aggregation. There was a 5-fold rise in the number of ME once the activated blood and lipid that were collected by the cardiotomy sucker passed through the reservoir. They also showed that the bubble oxygenator increased the number of ME generated by 2 to 3 times, when compared to a membrane oxygenator. Liu et al studies also seem to show that cardiotomy suction produced lipid ME, while examining cellular element. Kaza et al have found that patients randomized to have cardiotomy suction rather than a cell-saver suction device have greater lipid ME at the end of CPB[151].

3.4. Detection of Microemboli release following Cardiopulmonary bypass

Many investigators have used a variety of methods to detect the ME generated and have focused on a number of different sites during cardiac surgery. The aorta, carotid artery, middle cerebral artery or even the retinal arteries have all been used to detect the ME. The methods can be direct or indirect. An early, indirect method was the “screen filtration pressure" technique of Swank[152] where the presence of micro aggregates in stored blood was measured by the pressure needed to push blood through a screen filter of a given pore size. Other indirect methods include the Coulter counter[153] that measures micro particles of 0.4 to 800μm in diameter, again in-vitro. It has been criticised for measuring only at a single time point and not being able to measure gaseous ME or to continuously measure ME.

Investigations looking for direct evidence of ME to the brain, occurring during bypass are based on:

- Histological examinations
- Retinal angiography
- TCD

3.4.1. Histological examination

Moody et al[154] and other workers have used histological means to examine the brains of animals and humans following cardiac surgery to study the evidence of ME. Moody was the first to report small capillary and arterial dilatations (SCADs) in the autopsy brains of patients post-cardiac surgery. Although SCADs are exclusively seen in cardiac patients their actual cause remains unknown. It is thought that these SCADs are the "footprint" left behind mainly due to lipid ME when the solvent, alkaline phoshatase staining technique used in preparing the sections of the brain, has removed the actual embolic material.

3.4.2. Retinal angiography

Investigators such as Blauth et al[153,155,156] have used the retinal circulation as a visible extension of the cerebral microvasculature. They used the photographic technique of retinal fluorescein angiography to demonstrate retinal microvascular occlusions consistent with retinal ME. They also found that retinal microvascular occlusions were more common in patients with NP deficit. This is an invasive technique compared to TCD and it does not allow continuous monitoring for ME. Retinal fluorescein angiography can detect the effect of ME only at discrete time points. Although Blauth et al did develop a method to quantify the ME producing the occlusions, this technique did not gain popularity.

3.4.3. Transcranial Doppler

Transcranial Doppler (TCD) is the most commonly used non-invasive method for detecting ME in 'real time' and to investigate blood flow within the intracranial cerebral arteries. In order to obtain a TCD trace, the probe is placed against the skull above the zygomatic arch and the ultrasonic beam directed at the blood flow in the middle cerebral artery. In about 10% of the people it has not been possible to isonate the middle cerebral artery through the temporal bone because of varying thickness of the bone. The acoustic properties of embolic material, gaseous or particulate, differ from blood so that the emboli reflect the ultrasound more strongly than blood, producing a distinct pitch. It is these pitch changes or an embolic signal defined as a short duration signal, with an intensity 10db greater than the background and associated with a characteristic 'chirp' that produce the audible sounds called "High Intensity Transient Signals" (HITS). In fact, it allows continuous "live" monitoring of ME along with blood flow velocity. Of the three main intracranial arteries, the middle and anterior cerebral arteries are the terminal arteries of the ipsilateral internal carotid artery. Wijman et al[157] has shown that the middle cerebral artery is easier to isonate to detect HITS when compared to the anterior cerebral artery, being a bigger calibre vessel and the most accessible through the window of thinner bone in the temporal bone. The number of ME detected is probably related to the proportion of cerebral blood flow within each artery.

These HITS detected by TCD have been shown to correspond to ME made of air, platelets, fibrinogen or atheroma in laboratory in-vivo experiments[158,159]. Blauth et al disapprove of TCD since the number of HITS may not exactly reflect the number of emboli if automated counting is carried out. But the same criticism would apply to any other method mentioned earlier that does not have the same continuous “live” detection capability of ME that a TCD has. Therefore, in order to standardize the detection of ME, either gaseous or solid material, and make studies comparable, a number of recommendations for detection and recording have been made by the International Consensus Group (Ringelstein and associates in 1998)[160].

Padayachee et al[56] in 1987 were the first to use TCD during cardiac surgery. They detected embolic signals or HITS in 22 out of 27 patients at the time of aortic cannulation and in all patients during CPB using bubble oxygenators but none with membrane oxygenators. TCD as routinely used is able to detect both solid and gaseous ME, but cannot distinguish between the two. Since then, most investigators have continued to use TCD as the preferred method for detecting intra-operative ME despite its inability to differentiate between gaseous and particulate matter, even though recent researchers like Russel and Brucher[161] have suggested that distinction may be possible. This distinction is necessary to investigate the pathological sequelae of differentiating emboli. Other issues such as uni or bilateral isonation of the middle cerebral artery have also been studied. The 2001 study of Moser and co-workers[162] of unilateral verses bilateral monitoring of cerebral ME in 29 patients found only a 4% difference between sides and has shown that unilateral monitoring are sufficient when the goal is to characterize a given subject’s ME load. Therefore, the number of ME detected by TCD may be related to the proportion of cerebral blood flow.

A recent study by Markus et al[163] used a novel Embo-Dop system, using insonation at 2-ultrasound transducer frequencies system. They compared the gaseous embolic signals obtained in 7 patients with known patent foramen ovale by intravenous injection of agitated saline injections, with solid embolic signals that were obtained in patients with symptomatic carotid stenosis (N=23). The Embo-Dop dual-frequency system suggested better discrimination than a simple intensity threshold but it was found not accurate enough for use in clinical or research studies. They, therefore, suggested further work was required in order to develop reliable clinical systems for discrimination of emboli. The clinical importance of the distinction lies in the probability that the 2 types of emboli have different pathological effects.

3.5. Timing and generation of ME -- variables

3.5.1. Perfusionist

The perfusionist has been shown to play a part in the release of ME by Taylor and colleagues 1999[164]. The CPB circuit consisted of a soft shell venous reservoir, a hollow-fibre membrane oxygenator and a 32-micron arterial filter. The mean embolic rate was calculated for three time periods: 1) during surgical interventions (aortic cannulation and decannulation, cross-clamp application and removal, at initiation and end of CPB and start of cardiac ejection); 2) during perfusionist interventions (blood sampling and drug administration into the venous reservoir) and; 3) during baseline (all other time periods during CPB). The number of emboli per minute was significantly higher ($p<0.001$) during perfusionist interventions (6.9+/-4.5) than during surgical interventions (1.5+/-1.5) or during baseline (0.4+/-0.5). It was suggested that drug administration resulted in a higher embolic rate than blood sampling and these emboli were likely to be air bubbles that are not eliminated by the arterial line filter. Borger et al[165], in a 2002 study have also confirmed this.

3.5.2. Surgical manipulations

Surgical techniques can vary from surgeon to surgeon and also from one institution to another. This may also play a role in the release of embolisation during different aspects of the surgical procedure during CABG. Several studies by Barbut and co-workers demonstrated that nearly 60% of all emboli happened during clamp manipulation of the ascending aorta and following the release of cross-clamp[99,166,167].

Numerous events during surgery may also be associated with the timing of the ME:

- Chest opening
- Purse-string application prior to aortic cannulation -- full thickness bite
- Aortic cannulation
- Start and end of CPB
- During CPB, longer bypass time
- Cross-clamping of aorta
- Cardioplegia delivery, cannulation at root
- Lifting of the heart, during distal anastomosis
- Single/multiple partial aortic clamp, during top-end anastomosis

- Decannulation of aortic cannulae

Embolisation primarily takes place as a result of aortic manipulation during palpation, cannulation, cross-clamping, proximal coronary anastomosis and decannulation and possibly secondary to ‘sand blast’ effect from high-velocity jet existing from the aortic cannulae.

Barbut et al[99] in 1994 studied 20 patients undergoing CABG. They noticed that embolic signals were detected in all patients, but in 34% microembolic signals were detected as aortic cross-clamps were removed and in 24% when aortic partial occlusion clamps were removed. Only 5% were detected at the initiation of the bypass. Rates for embolisation were 15.15 embolic signals per minute at cross-clamp removal, 10.9 embolic signals per minute at partial occlusion clamp removal and fewer than 3 embolic signals per minute at other times. Correlation was found between the number of emboli and severity of aortic atheroma and NP deterioration. They suggested from the study that ME were associated with aortic cross-clamp release.

Other studies by Aranki[168] (1994) and Bertolini[169] (1997) have pointed out that partial occlusive clamping of aorta might act as a source of atheroembolic release leading to neurological dysfunction.

Baker et al[170] 1995 studied patients, comparing release of ME in three different blood cardioplegia techniques; cold antegrade (n=20), warm antegrade (n=17) or warm retrograde (n=20) cardioplegia. Continuous monitoring was divided into stages: Aortic cannulation, initiation of CPB, aortic cross-clamping, aortic declamping and decannulation until chest closure. The embolic events ranged from 22 to 2,072 per patient and were similar among groups. The rate and total at each stage were also similar. Total embolic events were highest during aortic clamping while the rate was highest at the initiation of the bypass. ME events were higher in the warm retrograde group than both antegrade groups during aortic declamping.

Benaroia et al[171] 1998 prospectively studied 32 first-time CABG patients. They analysed the number of ME in the middle cerebral artery (MCA) during CPB to see if it correlated with the blood velocity or the direction of flow as determined by the shape and size of the aortic cannula. Three aortic cannula types were used: 24F curved (n=19), 24F straight (n= 6), and 22F straight (n=7), with internal diameters (IDs) of 7.2, 6.6, and 5.9 mm, respectively. They concluded that neither blood velocity nor the shape or size of the aortic cannulae mattered with respect to the number of cerebral ME.

Grega et al[172] 2001 analysed 461 patients in a non-randomized study operated by a single surgeon in two groups looking at neurological and neuropsychological outcomes comparing single vs double-clamp technique. They were able to detect a significant improvement in neurological injury, reduction in the incidence of stroke and duration of hospital stay in the single clamp technique patients.

The study by Hammon and colleagues[173] of 395 patients has also shown a significant difference in NP outcomes when using single-clamp technique, venting of left ventricle and screening of ascending aorta using transoesophageal and epiaortic scanning.

Tsang et al[174] 2003 in a prospective randomized study demonstrated a significant decrease in the relative risk of adverse cerebral outcome without compromising myocardial protection with the use of a single aortic cross-clamp technique. They recommended that the use of the aortic side clamp should be avoided to minimize the handling of the ascending aorta, which could be a significant risk factor for embolic strokes following CABG.

Martens et al[175] 2004 in a prospective randomized study of 77patients undergoing CABG compared the amount of debries released using intra-aortic filtration during the automated proximal anastomosis device (GroupI,n=38) and conventional handsewn (Group II,n=39) technique and found that the number of particulate debris being released and captured on the intra-aortic filter was the same regardless of the technique used. The neuropsychological tests did not reveal significant differences between groups. In Group I, eight patients showed a decline of 20% or more on at least two tests (20.5%), compared to six patients in Group II (15.8%).

3.5.3. Post-surgical factors

Rewarming rate

Grigore and co-workers[84] in a prospective study involving 165 patients undergoing CABG showed that slower rewarming during CPB was associated with better cognitive performance at 6 weeks.

Low cardiac out-put state

As discussed in the previous chapter ‘‘global hypoperfusion’’ plays a role in cerebral dysfunction whether it occurs during or after surgery. Poor LV function or an episode of left ventricular failure is thought to be associated with a poor neurological outcome post-operatively[60].

Post-operative atrial fibrillation

Stanley and co-workers[174] from the Duke Heart Centre studied the role of post-operative atrial fibrillation to NP dysfunction. Out of 411 patients, 308 completed both pre and post-operative cognitive testing, 69 patients (22%) had post-operative atrial fibrillation. Those who developed atrial fibrillation showed more cognitive decline 6 weeks after surgery than those who did not develop post-operative atrial fibrillation (P=0.036).

3.6. Influence of atheroma load on cerebral microembolism

The Neurologic Outcome Research Group (NORG) from the Duke Heart Centre evaluated the ascending, arch and descending aorta of 128 patients to determine the aortic atheroma burden. They were able to demonstrate a significant but weak relationship between TCD-detected cerebral emboli and the atheromatous load in the ascending and aortic arch using TOE. Atheroma load was found to be greatest in the descending aorta and least in the ascending aorta. They concluded by showing that the embolic load was significantly associated with atheroma in the ascending aorta (p=0.013), while there was no association between emboli numbers and descending aorta findings[177].

Another study by Bar-Yosef et al[178] compared the relationship between aortic atherosclerotic disease and neuropsychological outcome following CABG. They compared TCD findings with TOE along with pre and 6-week post-operative NP assessment in 162 (81%) patients out of 201. They found no significant relationship between NP dysfunction and atheroma load in the ascending, arch and descending aorta. They concluded by saying that the aetiology of NP dysfunction is likely to be multifactorial and that aortic atheroma may not be the primary cause.

A limitation of both these studies is that they used TOE to evaluate ascending aortic atheroma. A study by Konstadt et al[124] showed that EAU is more sensitive and more likely to detect a greater degree of atheroma than TOE in the mid-ascending aorta up to the proximal arch, since large sections of the ascending aorta are not visible on TOE due to interposition of the trachea and the left main bronchus.

There was clearly a need for a study analysing the correlation between the atheroma load using EAU of the ascending aorta with the embolic cerebral load using TCD and this was incorporated in my study design.

3.7. Is the number of ME related to NP outcome

Although ME may not cause any immediate symptoms in patients, there is evidence to show that NP changes are noticed whenever a significant number of ME enter the cerebral circulation.

Pugsley et al[179] in 1994 studied the incidence of ME in the middle cerebral artery using TCD and NP outcome in a randomized controlled group involving 100 patients undergoing CPB surgery. Fifty patients having surgery using a 40μm arterial line filter had less ME counted than the non-filtered group. More patients from the non-filtered group had significant NP deficits at both 8 days and 8 weeks in the post-operative period.

Musumeci et al[10] in a randomized study involving 100 patients undergoing elective CABG surgery compared CA vs ICCF techniques as two different myocardial protection techniques and found no correlation between the total number of ME and NP outcome. They did notice slight deterioration in the Luria Nebraska Neuropsychological Battery (LNNB) tests for motor, visual, reading, memory and intellectual testing at 1 week but this recovered in all patients at 6 months.

Others such as Sylivris et al [13] investigated to verify whether ME signals correlated with early NP deficits and to identify, using magnetic resonance imaging (MRI) scans, whether radiologic evidence of cerebral infarction correlated with microembolic numbers during the bypass period. This study involved only 41 patients of which only 32 had NP testing. The NP testing was performed early at 5 or 6 days post-surgery. A total of 28 patients had both intra-operative TCD monitoring and pre-operative and post-operative MRI scanning. Of the 28 patients, 5 had evidence of cerebral infarction on MRI scanning and 23 had no evidence of stroke. TCD monitoring confirmed that most ME occurred during CPB. A significant early NP deficit after CABG did correspond to the total microembolic load during the bypass (p=0.008). However, there was a significantly higher ME load before surgical incision of the ascending aorta in patients with cerebral infarction detected by MRI scanning (p<0.0001) and not during the bypass period. This same relationship was not present in patients who had NP deficits post-operatively. Despite this, an analysis of the overall group showed that MES during bypass (rates and total counts) were not significantly higher in the MRI stroke group compared with the non-stroke group. Their study concluded by showing that microembolic load during bypass is associated with early NP deficits. In contrast, patients who showed evidence of strokes during bypass surgery had a higher microembolic load during the pre-incision phase than those without cerebral infarction. Differing mechanisms may be responsible for these different outcomes.

Fearn et al[180] studied 70 patients undergoing CABG with TCD to measure ME and middle cerebral artery blood velocity along with NP assessments which were conducted pre-operatively and at 1 week, 2 months and 6 months post-operatively. They found a weak but significant ($p<0.02$) correlation between emboli and a reduction in "overall memory reaction time" at 1 week post-surgery. In 40 patients, they detected more than 200 emboli, mainly during aortic cross-clamping and release, on initiation of bypass and finally while defibrillating the heart. Their study was also the first to report differing cognitive effects from emboli and hypoperfusion.

Some investigators have questioned whether there is a relationship between ME count and certain surgical interventions with regard to the NP outcome. Jacobs et al[46] in a small study involving 18 patients undergoing CABG examined the relationship between ME, NP and cerebral glucose metabolism. In addition, in 2 patients who also underwent valve replacements, the ME count was even higher. Overall, they found no correlation between the number of HITS, NP outcome or global cerebral glucose metabolism. The significance of this study is doubtful because of the small number of patients involved.

Mullges et al[181] in 2003 analysed 60 patients undergoing CABG randomized to either using a short or long aortic cannula in the ascending aorta. All patients had 1-2 days pre-operative and serial post-operative NP assessment (7 tests) on days 3, 6 and 9. The examiners were blinded from knowing what type of aortic cannulation was used. Only 32/60 patients had intra-operative TCD and NP assessment and 54/60 had 9th post-operative NP assessment. In the 32/60 patients, they were able to show a marked reduction in the number of ME in the short cannula group compared to the long cannula group (median 174.5 vs 413.0; p=0.011). They did not find any influence on early post-operative NP outcome.

More recently Stygall et al[182] in a longitudinal study of cognitive function after CABG examined 107 participants using 11 tests, pre-operatively and at 6 days, 8 weeks and 5 years after surgery. The overall NP change score declined at 6 days, showed some recovery at 8 weeks and declined again at 5 years. The number of ME recorded during surgery, post-operative short-term cognitive change and degree of recovery at 8 weeks were identified as predictors of change in NP score to 5 years. The authors point out that the number of ME detected may simply reflect the extent of the patients' cerebrovascular disease. Therefore, as an alternative theory to ME causing the decline, ME could be a feature of those who will decline anyway.

Recent interest in off-pump surgery has led investigators to see whether there are any NP outcome differences between on and off-pump coronary bypass surgery. Diegeler et al[183] conducted a randomized study in Leipzig involving 40 patients (20 in each group). They showed a significant difference in the ME count and post-op NP outcome on day 7 in the on-pump group, suggesting that cognitive dysfunction seems to have a strong correlation with ME generation due to CPB. A small study by Malheiros et al[184], however, showed a significantly lower ME count in the off-pump group (p<0.0001) with a longer bypass duration in the on-pump group. Inspite of this difference, they were unable to detect any NP differences between the two groups. Clearly an adequately powered study of much larger size is needed in this area.

In a randomized larger study involving n=281 patients (On=139, Off=142) by Van Dij et al[185] from Netherlands studied NP outcomes at 3 and 12-month intervals. Ten NP tests before and after surgery were assessed. Quality of life, stroke rate and all-cause mortality at 3 and 12 months were secondary outcome measures. The overall standardized NP change score at 3 months was p=0.03 and 12 months p=0.09 showing no significant differences. No significant differences were noted in the secondary outcome measures either. The same author[186] more recently at the 5-year follow-up confirmed that off-pump coronary surgery had no added benefit effect on 5-year cognitive or cardiac outcomes. This was also shown to be the same in a much recent randomized follow-up study by Stroobant et al[187] at 3 to 5 years after the CABG (n=74) surgery. They showed no significant difference in NP outcomes between on and off-pump CABG patients, indicating that the cardiopulmonary bypass may not be the main cause of late NP decline. This was also shown in a recent analysis of the Revascularization On versus Off Bypass (ROOBY) trial data of 1156 patients, only 1 of 9 neuropsychological outcomes at 1year following surgery favoured the off bypass group[234].

3.8. Summary

In summary, all the above studies suggest that there is more than one factor that is responsible for generating ME that can ultimately have an impact on the NP outcome. Although very few studies have found an association between the number of microemboli generated during surgery and neuropsychological outcomes, for two reasons. First the constitution and size of the microemboli are likely to be more closely related to neuropsychological outcomes than the absolute number of microemboli generated.Second, the functional impact of these microemboli might also depend upon the extent of pre-existing vascular disease in the brain.

With this in mind, in our next chapter we will investigate whether there is any relationship between microemboli (ME), comparing ICCF and CA as the two myocardial protection techniques and NP outcome.

Chapter 4

Role of myocardial protection techniques in the neuropsychological outcome during cardiopulmonary bypass

4. Role of myocardial protection techniques in neuropsychological outcome during cardiopulmonary bypass

4.1. Introduction

Since the development of coronary artery revascularisation, CA has been the widely used technique of myocardial protection since the mid 1970's. CA has since been comprehensively studied using crystalloid or blood. But even so there are still a substantial number who prefer to use ICCF as it has been safely used in both low and high-risk patients[188]. Exponents of ICCF claim that the technique is simpler, allows the myocardium to be reperfused during the procedure and has the potential to result in shorter ischaemic and CPB times[189].

However, ICCF is associated with more handling and repeated clamping of the aorta. It has been argued that especially in the presence of atheromatous disease, this manipulation may cause plaque adhering to the aortic wall to break or rupture releasing debris (ME) into the systemic circulation, thereby causing a proportion of these ME to eventually find their way into the cerebral circulation, increasing the risk of neurological and NP outcome[109].

Until now there have been only a few studies comparing these two techniques and looking at them in terms of the NP outcomes. In this chapter, we will review literature looking into the historical background for any difference with regard to NP outcomes comparing ICCF with CA as the two forms of myocardial protection during CABG surgery using CPB as it forms the primary objective of investigation in this thesis.

4.2. Cardioplegic arrest

The principle of CA is to minimize cellular metabolism and maximize cellular energy preservation without causing myocardial injury while providing the surgeon with a still and bloodless field. In addition to variations in temperature and composition of cardioplegia, different perfusion strategies to maximize coronary distribution can be adopted. Simply arresting the heart reduces the myocardial oxygen demand by nearly 90%; by cooling the myocardium cold cardioplegia significantly reduces the remaining 10% myocardial oxygen demand. Warm and tepid blood cardioplegia, on the other hand is believed to preserve cellular enzymes system and limit the cellular swelling and limit myocardial oedema. Cardioplegia solutions are used to arrest the heart in diastole and provide metabolic support to the heart muscle after cross-clamping the ascending aorta. It can be infused as a crystalloid solution or mixed with blood. The ideal cardioplegic solution should permit immediate cardiac arrest. Cardioplegia solution may be infused continuously or intermittently. Continuous infusion is maintained at a constant rate during cross-clamp time, intermittent cardioplegia is infused every 20 minutes for a short period (2-3 minutes). These two techniques could be given separately or in combination. Routes of infusion could be via the ascending aorta (antegrade) or coronary sinus (retrograde). The major concern with the antegrade method is poor preservation of the myocardium distal to coronary occlusion or stenosis while with the retrograde method there are issues regarding adequate protection of the right side of the heart, in addition to involving the anti-physiological method of delivering the cardioplegia via the coronary sinus. In 1994, Hayashida an1 co-workers[190] used the antegrade combined with the retrograde technique, which showed a better distribution of cardioplegia into the myocardium.

4.2.1. History and background

Melrose et al[191] introduced cold hypertonic potassium citrate blood cardioplegia in 1955. Following reports of left ventricular damage it was not used in the United States for almost a quarter of a century. Investigation by Tyers et al[192] showed that the problem faced by the Melrose solution was inappropriate concentration of its constituents, rather than inappropriate composition. Numerous different cardioplegic solutions and methods of myocardial protection have been advocated since this date.

Prerequisites for clinical use of cardioplegia should include: 1) a solution that is shown to be safe; 2) assurance of even distribution to all areas; 3) periodic replenishment to counteract non-coronary collateral washout and; 4) strategies for delivering and maintaining cardioplegia that can be adaptive to various clinical conditions.

4.2.2. Effect on the NP and myocardial outcomes

Although cardioplegic arrest is thought to cause less cerebral and NP dysfunction since this technique involves less handling of the aorta, there is still controversy regarding this technique and its relationship to NP deficits. Martin et al[193] analysed 1,001 patients who were randomized to have continuous warm retrograde cardioplegia and normothermic systemic perfusion during CABG or hypothermic cold antegrade cardioplegia and noticed a significantly higher incidence of neurological and peri-operative cardiovascular problems in the first group.

Baker AJ[170] and colleagues in Toronto, Canada, using 3 different CA techniques (cold antegrade, warm antegrade and warm retrograde) detected a significantly greater number of

ME in the warm retrograde group than the cold antegrade ($p<0.01$) and warm antegrade ($p<0.001$) groups. This suggests more chances of neurological events occurring because of it. Therefore, with more ME being generated as discussed in the previous chapter this may have an influence on the NP outcome[179].

4.3. Intermittent cross-clamp fibrillation

ICCF is one of the earliest forms of myocardial protection techniques that is still being used in some centres today[194]. Despite its decreased popularity, it is considered to be safe, fast, simple and a successful alternative technique of preserving the myocardium during CABG using CPB by Korbmacker et al[106]. The heart is electrically fibrillated using topical electrodes prior to application of the aortic cross-clamp. This induces global ischaemia, followed by anoxic arrest and electrical silence on ECG. This technique depends on reducing myocardial oxygen demand by moderate systemic hypothermia (32-33°C), followed by simultaneous workload reduction by emptying the heart and inducing ischaemic preconditioning of the myocardium[104,195]. These short ischaemic periods, 15-20 minutes can rapidly be reversed by coronary reperfusion on release of the aortic cross-clamp. Following completion of the distal graft, the heart is defibrillated and the proximal anastomosis performed using a partial occlusive side-biting clamp.

4.3.1. History and background

Senning[196] in 1952 was the first to introduce a quiet, perfused heart using ventricular fibrillation and thereby avoiding intentional ischaemia. Subsequently, in January 1968, W.Dudley Johnson[197,198], from Milwaukee, USA, became the first to use intermittent ischaemic arrest as the form of myocardial protection technique in CABG. He believed that there were several advantages in using ICCF compared to CA while performing coronary revascularisation: 1) the ventricular regional wall contraction could be assessed immediately between grafting of coronary arteries using ECG, once the heart was reperfused and spontaneously beating. Using cardioplegia, this assessment could not be made as the heart is stopped for a longer period of time; 2) the longer period used for grafting in difficult cases was found to accentuate the benefits of the "ischaemic preconditioning" effect on the heart and; 3) cardioplegic solutions are rich in potassium and potentially may have damaging effects on the endothelium whereas with the ICCF technique once the coronaries are bypassed the segment distal to the blockage would get its blood supply in a more normal physiological form immediately once the aortic cross-clamp has been released.

4.3.2. Effect on the NP and myocardial outcomes

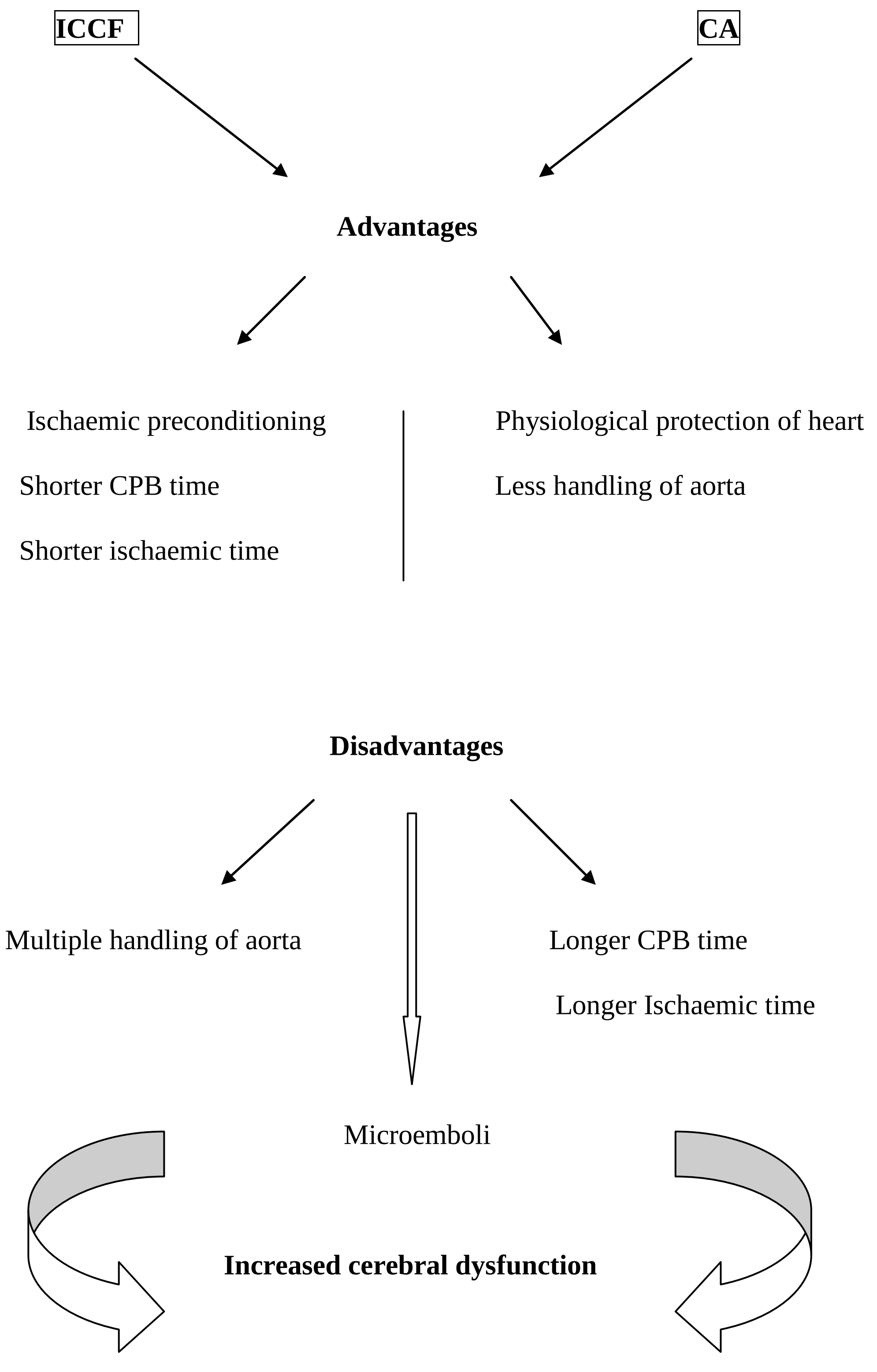
As ICCF involves repeated clamping of the ascending aorta during surgery, this technique could subsequently have a catastrophic outcome with regard to cerebral and NP functioning. However, Bonchek et al[196] reported only 1.1% transient and 1.8% permanent cerebral events in a series of 3,000 patients operated on with repeated aortic cross-clamping. Raco and co-workers[199] in 2002 analysed prospective data on 800 consecutive patients undergoing elective (n=520) and non-elective (urgent=226, emergency n=54) CABG using ICCF by a single surgeon. NP disorders were seen mainly in the non-elective patients with a total stroke incidence of 1.1% and TIAs of 0.4 % for all comers. This study suggests that ICCF is a safe technique with both elective and non-elective patients in the hands of an experienced surgeon.

Musumeci[10] and co-workers in a randomized study showed that in patients with no pre-operative evidence of aortic or cerebrovascular problems, repetitive clamping of the aorta in ICCF was not associated with a higher rate of cerebrovascular events, while comparing the single-clamp technique using blood cardioplegia. Some studies have suggested that the presence of atheromatous lesions markedly increase the risks[196,200]. Even the single-clamp technique used in cardioplegia with severe diffuse atherosclerosis would not be safe as shown by Aranki and co-workers[168].

The following studies have shown their myocardial benefits. By using more sophisticated methods of myocardium specific enzymes or proteins (Creatine kinase and Troponin I or T) to evaluate myocardial protection. Flameng et al[201] in a randomized clinical trial in 1984 assessed ICCF vs St. Thomas's Hospital crystalloid cardioplegia using Creatinine Kinase Isoenzyme MB (CKMB) assays and concluded that ICCF is as effective as cardioplegia in protecting the myocardium. Pepper JR[202] and colleagues in 1982 randomized 50 patients comparing cold St. Thomas`s crystalloid cardioplegia with ICCF. Using CKMB, left ventricular biopsies and post-op 12-lead ECG, they concluded that there were no differences while cross-clamp time was longer in the cardioplegia group. Anderson et al[103] in 1994 compared creatine Kinase MB isoforms and troponin T assays in 40 patients. CKMB 2 was found to be significantly higher in blood cardioplegia (n=20) compared to ICCF (n=20). Although troponin T (TnT) was raised in the cardioplegia group the difference was not significant. The randomized study of Taggart[104] in the 1994's and the retrospective analysis of Bonchek et al[188] on 3,000 first-time CABG patients using the non-cardioplegic technique have also shown ICCF to be safe and favourable.

Musumeci`s 1998[10] randomized study of 91 patients undergoing first time elective CABG concluded that CKMB, TnT and TnI (Troponin I) increased in both groups. The peak levels at 10 hours, 24 hours, and 96 hours post-operatively were higher in the blood cardioplegia group. This reached statistical significance at 10 hours with CKMB (p=0.021) and 10hours and 24hours with TnT (p=0.038 and p=0.027). Despite longer bypass and ischaemic time in the cardioplegia group it was not statistically significant.

4.4. Comparing the two techniques in terms of NP outcomes



The above chart compares the potential advantages and disadvantages between the two myocardial protection techniques.

With recent interest in ischaemic preconditionin, a review by Scarci et al suggests that intermittent cross clamp fibrillation may also have a preconditioning benefit on the myocardium when compared to cardioplegic arrest[203]. This has been seen in a laboratory based study on Wistar rats by Fujii[204] et al 2005 where there were evidence of a positive benefit between ischaemic preconditioning and ICCF technique. Nevertheless, a larger randomized clinical trial is still warranted.

Several randomized clinical trials (Musumeci 1998[10], Taggart 1994[104] and Anderson 1994[103]) have shown cross-clamp fibrillation to provide equal or even better cardiac outcomes when compared to CA.

The 1980's study by Pepper[202] and co-workers revealed no significant differences in their study group of patients with well-preserved left ventricular function, with regard to myocardial protection outcomes between the two techniques. These results were also confirmed by later studies conducted by Bonchek[196] and co-workers. Casthely [105] and co-workers using TOE also confirmed no difference in post-operative systolic and diastolic function between the two groups.

Other investigators such as Liu et al[105] 1998, Anderson et al[104] 1994, Cohen et al [206] 1997, Alhan et al[200] 1996 and Gerola et al[207] 1993 have also clearly and repeatedly demonstrated in prospective randomized trials that the technique of ICCF is equivalent to both crystalloid and blood cardioplegia in terms of clinical outcome and biochemical markers of myocardial injury.

Korbmacher et al[106] 2004 in a recent review article compared a meta-analysis of published data taken from international centres using ICCF technique. They suggested that with regard to neurological outcomes, despite repetitive clamping of the aorta especially in patients with no previous evidence of pre-operative aortic or cerebrovascular disease, there was no evidence of increased cerebrovascular events similar to Musumeci et al`s prospective randomized trial of single-clamp technique using cardioplegia vs ICCF[5] technique. This was also confirmed in another large retrospective study involving 2,000 primary cases showing no significant difference between cold blood cardioplegia and ICCF with regard to cerebrovascular outcome[105]. While some studies suggest using caution and other myocardial protection when there is evidence of severe aortic atherosclerosis[200,205].

Currently there is only one study by Musumeci et al 1998[10] comparing single-clamp cardioplegia against ICCF, examining the impact of repetitive aortic handling during CPB on the generation of ME and its relationship on neurocognitive outcome. They detected no statistical difference in the number of ME and neurocognitive deficit between the two myocardial protection techniques. However they did notice a difference in the pattern of ME release. ME occurred mainly during surgical manipulation during total and partial clamping of the aorta in the ICCF, while a continuous low-grade production of ME with a larger shower occurring when the aortic cross-clamp was removed was noticed in the single-clamp cardioplegia technique.

4.5. Discussion

All the evidence shown by several studies discussed in this chapter ranging from invasive (blood cardiac enzyme/protein markers, muscle biopsies) to non-invasive (post-op ECG, TOE) outcomes or end-point to suggest that ICCF is safe or even equal to CA technique in providing adequate myocardial protection in order to safeguard the overall function of the heart. Despite several comparative studies between the two techniques there is still only one randomized study in the literature by Musumeci et al looking into NP outcomes.

Since all the above studies have suggested that ICCF is a safe myocardial protection technique to the heart, this randomized study was set up to find out the impact this alternative myocardial protection technique of ICCF might have with regard to NP outcomes when compared with the traditional CA technique because of its repetitive handling of the ascending aorta.

Chapter 5

Rationale for new study, methods and materials

5. Rationale for new study, methods and materials

5.0. Introduction

So far only one study by Musumeci and co-workers[10] 1998 have compared both myocardial and cerebral protection in a group of patients randomized to either single aortic cross-clamp technique n=43 (CA) or ICCF n=48. They detected no significant differences between the two groups on either number of intra-operative ME or post-operative NP performance. However, biochemical analysis did suggest that the ICCF technique afforded a more effective form of myocardial protection. Nevertheless, there are various methodological flaws within this study.

This study was considerably underpowered as there were only 70 participants available for the final follow-up at 6 months to detect a significant difference between the two groups: In NP performance too the body temperature and flow rate during CPB differed in each group. Those receiving cardioplegia were cooled to 28°C with a flow rate of 1.6 l/m^2 per min while the intermittent cross-clamp patients were allowed to drift to 34°C and flow maintained at 2.4 $l/m^{2.}$per min. This could be potentially problematic, as hypothermia has been employed as a means of cardiac and cerebral protection throughout cardiac surgery history. In addition, this study excluded patients with aortic disease and this may have reduced the impact of repeated cross-clamping in ICCF and resultant ME production, thereby producing a confounded result.

5.1. Study overview

This chapter describes in detail the objectives, methodologies and results of a single-centre double blinded randomized clinical study undertaken by the author in collaboration with the Departments of Cardiothoracic Surgery, Anaesthesia, Neurology and Psychiatry at the Heart and Middlesex Hospitals, London, between February 2002 and December 2004.

5.2. Descriptive Title

A randomized clinical study to examine the effects of ICCF and cardioplegia with regard to the NP outcome during CABG surgery along with detection of ME generation using TCD and screening of ascending aorta for atheroma using DP,TOE and EAU during the procedure.

5.3. Hypothesis

It is proposed that the use of ICCF, through manipulation of the aorta is thought to be associated with increased microembolisation (ME). A higher burden of ME is thought to be associated with a worsening NP outcome; Therefore ICCF was hypothesised to have a poorer NP outcome than CA.

5.4. Study objectives

The primary objective of this study is aimed at comparing the occurrence of intra-operative ME and post-operative change in NP performance in patients undergoing CABG surgery using either ICCF or CA as a method of myocardial protection.

The secondary objective is to compare intra-operative screening techniques of the ascending aorta using DP, TOE and EAU in the detection of atheroma to (1) compare the proportion of patients identified as having atheroma by these 3 screening techniques, and

(2) examine whether the 3 techniques identified the same patients as having aortic disease.

5.5. Ethical approval

The study was conducted in accordance with the provisions of the Declaration of Helsinki (amended 1989) and with the approval of the University College London (UCL) Hospitals Ethical Review Committee of Human Research.

5.6.Sample size planning

The sample size power calculation based on Z change score was founded from a previous study conducted by Arrowsmith et al at the institution of the present investigation based on the number of patients needed to detect a significant difference in neuropsychological deficit, which was the primary outcome measure of the trial. The incidence of deficit was estimated to be 20%[9]. The sample size required was 74 per group that is a total sample of 148 calculated to give adequate power (a 90% chance) to detect a 20% reduction in neuropsychological deficits at the 5% level. It was estimated that a 20-25% loss to follow-up was possible therefore it was calculated 200 participants were required to result in an adequately-powered study.It was assumed that there would be equal size and equal variance for the control and treatment groups, using the formula below.

Sample per group = $2*[Z\,(1-\alpha) + Z\,(1-\beta)]^2 / \Delta^2$

Δ^2 represents the standardized difference (i.e. the treatment divided by its standard deviation)

5.7. Study population

Patients who were on the elective waiting list from home and in-patients' list for urgent CABG surgery were invited to take part in the study in the Department of Cardiothoracic

Surgery at the Middlesex/ Heart and University College Hospitals NHS Trust.

5.8. Recruitment and consent of patients

Patients fitting the criteria were invited to participate. In accordance with ethics committee guidance, fully informed consent was obtained from all patients. The study was explained verbally to patients who were then given a written information sheet to read (see **Appendix 8.1**). Patients were requested to sign a consent form if they agree to participate (the consent form was part of the Patient Information sheet / Informed consent form, see **Appendix 8.1**).

A brief medical history and clinical examination along with a record of current medication were noted. Each patient was then enrolled into the study and identified by a unique patient identification number starting from ‘001’.

5.9. Inclusion criteria

1. All patients over the age of 18 years and willing to participate.
2. Case referral-elective and urgent CABG.
3. First-time CABG or Re-do CABG.
4. Patients fluent in English.
5. Good visual and auditory acuity.
6. Patients over the age of 80 years. Although these patients are at most risk of NP injury, they also have the highest co-morbidity and mortality, which may make them less likely to attend follow-up.

5.10. Exclusion criteria

Patients were excluded from participating in the study if any of the following exclusion criteria was met.

1. Existing or prior cerebrovascular disease and previous psychiatric illness.

2. Unable to understand English.

3. Unable to write or use the keyboard due to physical disability.

4. Evidence of intra-cardiac thrombus.

5.11. Randomization

Two hundred and twenty envelopes containing 110 ICCF and 110 cardioplegia group were given to the perfusion department. On the day of the operation, the chief perfusionist in the presence of his assistant and the author would open the randomization envelopes (patients were blinded for treatment group assignment, all the investigators were subsequently blinded during analysis of all data). The operating surgeon would then be informed regarding the type of myocardial protection technique to be used after setting up the appropriate bypass circuit. When a patient had to be removed from the study because of failure to adhere to the protocol their allocated envelope was not re-used (e.g. surgery done off-pump) and these envelopes were marked as cancelled.

5.12. Theatre protocol

A standardized protocol developed from previous NP studies assessing outcomes post-cardiac surgery involving anaesthesia, surgical technique, cardiopulmonary bypass, control of blood pressure, mean perfusion pressure and control of pH was followed.

5.13. Anaesthesia

Using a standardised anaesthetic technique as used in most cardiac patients an hour prior to surgery, patients were given premedications consisting of 10-20mg Temazepam or Diazepam 5-10mg as per the anaesthetist's preference. Oxygen as a supplement was given via a facemask at a rate of 4 l/minute starting from the time the premedication was commenced until induction of anaesthesia. Following conventional central venous and arterial line insertion, intervenous induction was commenced using fentanyl 5-10mcg/kg , propofol 0.5- 10mg/kg , or etomidate 0.05-0.1mg/kg and pancuronium 0.1mg/kg. Intubation was then carried with a number 7.0 or 8.0-cuffed endotracheal tube and ventilated with isoflurane (0-2%) in oxygen and air.

The patient was intubated with a cuffed endotracheal tube and the lungs mechanically ventilated. Antimicrobial prophylaxis was then administrated. This usually consisted of Flucoxacillin and gentamycin or erythromycin in patients who where allergic to penicillin.

A transcranial Doppler probe was than placed over the right zygomatic arch after urinary catheterisation and placement of a nasopharyngeal continuous temperature probe. Following this a transoesophageal echo probe was inserted into the oesophagus and the patient was subsequently transferred into the operating theatre.

5.14. Cardiopulmonary bypass (CPB)

CPB was established between single right atrial and ascending aortic cannulae, non-pulsatile flow was used throughout the bypass period using a roller pump. The cardiopulmonary circuit consisted of a hollow fibre membrane oxygenator (Quantum HF-6700 BardLtd) and arterial filtration line (33μm, Bard Ltd Prim-VuTM, Bard Ltd). The bypass circuit was primed with 1.6 litres of Hartmann's solution heparinised with 5000 IU of sodium heparin. Full anticoagulation was achieved prior to aortic cannulation with 300 IU/Kg heparin. Further doses of heparin were given throughout CPB and activated clotting time (ACT) was maintained greater than 400 seconds. The flow was maintained at 2.4 l/min/m 2, reduced to 75% when full core cooling to 32-34°C was achieved. Mean arterial pressure was maintained as close to 50mmHg as possible while on bypass. Using appropriate vaso-active drugs either constrictors (phenylephrine) or dilators (phentolamine) were administrated to achieve this.While on CPB patient was maintained on propofol infusion 1-2mg/kg along with actrapid 0-5units/h (adjusted to control blood sugar). Acid-base regulation during CPB was carried out using the alpha-Stat protocol. At the end of CPB the anticoagulant effect of heparin was reversed with protamine sulphate to correct the ACT to pre-CPB levels.

5.15. Myocardial protection technique

Patients were randomized on the day of surgery to either ICCF or cold blood cardioplegia as the technique of myocardial protection. Depending on the randomization, patients in the ICCF group had their distal anastomosis constructed during brief periods (10-15 minutes) of aortic cross clamping and ventricular fibrillation. Once each distal anastomosis was completed the aortic cross-clamp was released. If the heart failed to revert spontaneously into sinus rhythm then it was cardioverted using 10-20 joules using the internal paddles. The proximal anastomosis was finally completed using a partial side-biting clamp. This sequence was repeated as per the number of grafts needed by individual patient requirements.

In the cardioplegia group, myocardial protection was achieved using 1 litre of antegrade cold blood cardioplegia (based on St.Thomas`s Hospital 1 solution). Further doses were infused at a rate of 150 to 200ml/minute at every 30-minute intervals. Once all the distal anastomoses were performed the cross-clamp was removed, the proximal anastomosis was then completed using a single side-biting clamp. All the vein grafts, irrespective of which myocardial protection technique was used, were carefully de-aired using a 25G needle.

5.16. Intra-operative monitoring

The author recorded the entire standard monitoring of mean arterial pressure, systolic and diastolic blood pressure (BP), and nasopharyngeal temperature, atheroma screening findings from DP, TOE and EAU and TCD recordings during various stages of the surgical procedure himself. (**Appendix 8.3**) In addition to transcranial Doppler monitoring there were specific intra-operative variables that have a potential influence on ME generation and NP outcomes were also recorded.

They included:

1. Clinical presence of aortic atheroma or calcification -- chest X-ray.

2. Intra-operative screening for atheroma in the ascending aorta -- DP, TOE and EAU.

3. Minimum temperature on CPB.

4. Maximum temperature reached following rewarming.

5. Duration to rewarm to 37°C.

5.17. Neuropsychological Test Protocol

5.17.1. NP assessment test (pre and post-operative tests)

All patients underwent neuropsychological testing by a single experienced psychologist on two occasions (i) preoperative assessment (twenty four to forty eight hours before surgery) and (ii) six to eight weeks after surgery. The patients were brought from their wards to the same room where tests were carried out under relaxed conditions.

The *New Adult Reading Test [NART]* (Nelson and O'Connell 1978[194]) was undertaken pre-operatively to obtain an estimate of premorbid IQ.

The battery of 9 NP tests chosen to cover a range of domains as detailed below had been developed at UCLH and included the core battery as recommended by the consensus meeting in 1995[195]. The tests selected are widely used in literature on CABG and have been shown to be sensitive to change following cardiac surgery (Pugsley et al[179] 1994) well-normalised and can be performed in the limited time available without disruption of clinical procedures.

Where available, parallel forms were administered to limit the effects of learning between assessments. The battery consisted of:

5.17.1.1. The Rey Auditory Verbal Learning Test [R-AVLT] (Rey 1964[210])

This widely used test involves free recall following the repeated verbal presentation of a 15-word list. The same list is repeated 5 times with free recall after each presentation. This sequence is followed by a presentation of a second (distractor) list followed by free recall. Immediately following this, the participants are required to recall as many words as they can from the first list without a further presentation (delayed recall). The total number correctly recalled over the first 5 trials (verbal learning) and the change between trials 5 and 7 (delayed recall) were recorded.

5.17.1.2. Non-Verbal Recognition Memory Test [NVRM] (Pugsley et al 1994[179])

This is a computerized timed recognition memory test in which 1 checker-board design is presented on a computer screen for 10 seconds and followed by 3 designs. The task is to identify which of the three designs is the same as the previous one as quickly as possible. The task consists of 20 presentations, with the total response time being recorded.

5.17.1.3. Trail making A [TMTA]

This and the following test originally formed part of the Army Individual Test Battery[211] (1944) and assess motor speed and attentions. Test A involves the participant in drawing lines, as quickly as possible through consecutively numbered circles. Time to completion was recorded.

5.17.1.4. Trail making B [TMTB]

This is a parallel task to TMTA but more difficult, as it involves alternating between ascending numbers and letters. This test measures not only motor speed and attention but also mental flexibility.

5.17.1.5. Letter Cancellation Test [LCT] (Talland and Schwab 1964[212])

This paper and pencil task consists of cancelling a random target letter from rows of letters. Performance was scored on time to completion.

5.17.1.6. Symbol Digital Replacement Test [SDRT] (Pugley et al 1994[179])

This is a computer driven task adapted from the paper and pencil version devised by Smith (1968, 1973). This requires the participant to pair 45 pre-coded digits with symbols. The score was time to completion.

5.17.1.7. Choice Reaction Time Test [CRT] (Pugsley et al 1994[179])

This is a computerized task in which participants are required to discriminate and respond as quickly as possible to two letters (A&B) which are displayed randomly on a computer screen. Mean response time was recorded.

5.17.1.8. Grooved Pegboard Test – Dominant [GPD] and Non-dominant [DPND]. Matthews and Klove 1964[213])

This timed test of manual dexterity and complex fine-motor co-ordination discriminates differences in right and left hemispheric performance. It consists of a small board containing a 5 x 5 set of slotted holes angled in different directions. Each peg has a ridge along one side requiring it to be rotated into position for correct insertion. The score was time to completion.

5.17.1.9 Mood State

In order to examine the impact of anxiety and depression on NP performance, it has become increasingly common for mood state to be assessed at each time of testing.

Depressed Mood: Center for Epidemiologic Studies Depression Scale [CES-D) (Radloff 1977[214]). This is a 20-item self-report measure for use in the general population studies to assess the presence and severity of depressive symtomatology.

Anxiety: Spielberger State and Trait Anxiety Inventory [STAI] (Spielberger et al 1983[215]). This questionnaire consists of 20 items for measuring trait anxiety and 20 items for measuring state anxiety. The trait measure (administered pre-operatively only) provides an index of personality based anxiety level whereas the state anxiety level provides a measure of anxiety in the current situation.

All tests were performed during the week pre-operatively (usually on the day preceding surgery) and then 6-8 weeks post-surgery. The pre-operative test was usually done the afternoon prior to surgery and the post-operative test on the day that the patient returned to the routine surgical follow-up clinic.

5.17.2. Transcranial Doppler

The author using a TCD (Nicolet EME Pioneer 4040, Uberlingen, Germany) monitored the microembolic events. The right middle cerebral artery (MCA) was isonated using a 2MHz pulsed wave transducer secured by a headband positioned on the right side of the skull just above the zygomatic arch between the lateral aspect of the eye and ear. The author did this prior to the skin incision since electrical (radio frequency) interference occurred during isonation from electrocautery. All measurements were made ‘off-line’ using international consensus criteria[160] and a second observer reviewed 10% of the tapes to assess inter-rater reliability.

Microemboli were counted throughout from cannulation to 15 minutes post-decannulation. Nine surgical events were noted:

Cannulation

Time of going on CPB

Cross-clamp on

Top-end anastomosis, side-biting clamp on

Top-end anastomosis, side-biting clamp off

Cross-clamp off

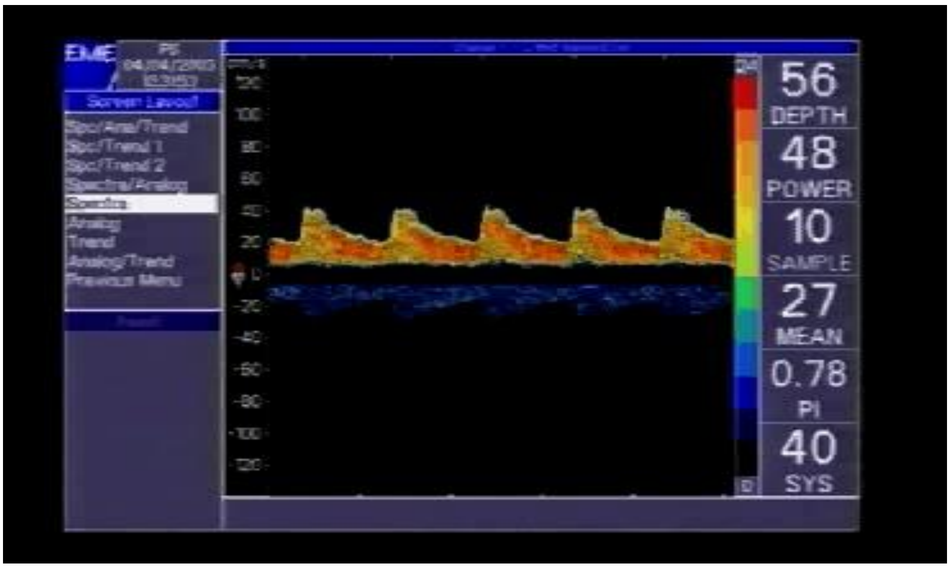
Coming off CPB

Decannulation

15 minutes post decannulation

In line with other researchers (Stroobant et al[15]) the number of ME detected within one minute was considered to be associated with that event[11,12,99].

Transcranial Doppler tracing of right middle cerebral artery



The Doppler loudspeaker was turned off during intra-operative monitoring so that the surgeon was blinded to the number and timing of the ME. Continuous transcranial monitoring was recorded from the start of the skin incision until 15 minutes after aortic decannulation. Video (VGA) signals from the TC4040 were converted to PAL format using an interface unit (Mediator, Video Logic, UK) and recorded in real time, with corresponding stereo audio signals on standard VHS videotape (AG6200, Panasonic, Matsushia Electric Co. Ltd. Japan).

A second observer Ms. Jan Stygall who was blinded to patient details and treatment group, reviewed 10% of the tapes to check inter-rater reliability.

5.17.3. Ascending aorta screening

As it was not a standard practice to routinely use TOE and EAU technique in assessing the ascending aorta during cardiac surgery at the Heart & UCL hospital. Following verbal and written consent as part of a general screeing protocol to this study the ascending aorta (which was divided into three segments as proximal, middle and distal) was screened for atheroma using three techniques: DP, TOE and EAU during the pre-bypass intra-operative period only to detect atheroma, grade their severity and to aid during the surgical manipulation of the ascending aorta for the whole group rather then individually (ICCF or CA).

5.17.3.1. Digital palpation

Once the pericardium was opened and prior to the harvest of the internal mammary artery, the surgeon digitally palpated the ascending aorta circumferentially from the innominate artery to the aortic annulus. The surgeon immediately described his findings, which were then recorded by the author. Simultaneously, the investigators (SS or AS) assessed the ascending aorta for atheroma with TOE using an ATL HDI 3000 machine with an MPT7-4 TOE probe (4-7MHz).

Atheroma was graded as follows:

<u>Grade score:</u>

Grade 0 -- Normal, no thickening felt

Grade 1 -- Abnormal, thickening felt

(Cannulation and handling of aorta was avoided in those abnormal sites depending upon TOE and EAU findings.)

5.17.3.2. Transoesophageal echocardiography

Using an ATL HDI 3000 TOE machine with an MPT7-4 probe (4-7MHz), all patients were assessed by the author and a second investigator Dr. Andrew Smith, Consultant Cardiac Anaesthetist in the theatre prior to CPB and immediately post-CPB in the theatre. The author paid particular attention looking at the following findings:

- ➢Assessment of the ascending and thoracic aorta
- ➢The overall left ventricular regional wall motion abnormalities

The ascending and thoracic aorta were graded and scored by author as follows:

TOE-1 Grade score: (Distal to left subclavian-thoracic aorta)

Grade 0 -- Normal, less than 1mm

Grade 1 -- Mild atheroma, 1 to 2mm

Grade 2 -- Moderate atheroma, 2 to 3 mm

Grade 3-Severe atheroma, more than 3 mm, or mobile atheroma

TOE-2 Grade score: (Proximal ascending aorta)

Grade 0-Normal, less than 1mm

Grade 1-Mild atheroma, 1 to 2 mm

Grade 2-Moderate atheroma, 2 to 3mm

Grade 3 -- Severe atheroma, more than 3mm or mobile atheroma

Left ventricular regional wall motion abnormality was assessed pre-bypass and post-bypass. They were scored as per the national echo board grading protocol. (**Appendix 8.3**) Due to difficulties in imaging portions of the ascending aorta with TOE, only the proximal portion of the ascending aorta near the annulus was screened.

5.17.3.3. Epiaortic ultrasound

Following the DP and TOE assessment, EAU was then used by the same surgeon performing the DP assessment to examine the ascending aorta for atheroma using a surface ultrasound P7-4 phased array probe (4-7MHz) with an ATL HDI 3000 machine (GE Healthcare, Bucks., UK). The probe was placed inside a sterile plastic sheath containing 20 to 50ml of sterile crystalloid solution. This acts as an interface to improve imaging of the anterior surface of the ascending aorta by eliminating air pockets. Attention was given to ensure that the sterile saline was free of any air bubbles. Approximately half to one centimetre of solution was left between the probe tip and the aortic surface.

The ascending aorta was scanned in its proximal (aortic annulus upto right pulmonary artery), middle (portion directly in front of the right pulmonary artery) and distal (from the right pulmonary artery upwards) segments from the aortic annulus to the base of the innominate artery.

The three aortic segments were scanned and atheroma graded as per a modified grading score devised by the author.

<u>Grading of aortic atheroma:</u>

Grade 0 -- Normal less than 1mm

Grade 1 -- Mild atheroma between 1 to 2mm

Grade 2 -- Moderate atheroma between 2 to 3mm

Grade 3 -- Severe atheroma more than 3mm or mobile atheroma

In total, 6 different surgeons were involved in the DP and EAU assessment. In each case, the surgeon performed the DP assessment and gave his findings before performing the EAU assessment. The EAU assessment findings were recorded before making the surgeon aware of the TOE findings. To aid offline analysis, the EAU assessment was performed in the same manner for each case.

Once the aorta was assessed, the surgeon following discussion with the author would modify any surgical cannulation or handling of aorta accordingly, thereby minimizing any chance of plaque disruption so as to reduce embolic events.

These ultrasonography findings were recorded on to a VHS tape for further assessment by the author and 10% of the tapes that were randomly picked by computer by a national board echo certified Consultant Anaesthetist Dr. Andrew Smith.

5.18. Demographic and other pre-operative data

Age, sex, race, body mass index, grades of angina and dyspnoea, history of myocardial infarction, hypertension, diabetes mellitus, hypercholestremia, peripheral vascular disease and smoking, elective or urgent referral, number of coronary vessel disease, left main stem disease, left ventricular ejection fraction, Parsonnet score (initially used and later changed over to Euroscore), Euro Score and pre-operative medication were all noted. (**Appendix 8.3**)

5.19. Intra-operative data

Operation time, intra-operative systolic and mean arterial pressure, time on CPB, cross-clamp time, number of grafts, type of conduits used -- long saphenous vein, internal mammary or radial artery -- screening of ascending aorta for atheroma, timings of aortic cannulation, initiation of CPB, application of cross-clamp, total cross-clamp time, removal of cross-clamp, application of top-end side biting clamp for proximal anastomosis, removal of side-biting clamp, cessation of CPB, total CPB time aortic decannulation, minimum and maximum temperature and time taken to rewarm from minimum temperature to 37ºC were all recorded. (**Appendix 8.3**)

5.20. Post-operative data

Once the patients were extubated and stable they were then assessed for any neurological and NP deficit. All relevant clinical findings were then documented. (**Appendix 8.3**)

5.21. Analysis of results Neuropsychological, Microemboli

Statistical analysis was performed using the Statistical Package for the Social Sciences Software (SPSS version 12.0. 1 for Windows). Univariate analyses were conducted using chi-squared analysis or Fisher's exact test where appropriate. To investigate group differences independent t-tests were performed on normally distributed continuous data and the Mann-Whitney test on non-normally distributed data, to correct for any ties in ranking the 'Z' value was reported instead of the 'U'. Due to the number of comparisons made and to avoid the likelihood of making a Type 1 error a significance value of $p = 0.01$ was set.

As a primary endpoint early studies investigating neuropsychological decline following CABG have rated the participants as either having or not having a deficit (reflecting both potential preserved learning ability and potential deterioration on the tests). This binary classification is insensitive and has the disadvantage of being unable to take into account any improvements in performance as they consider only deterioration. Therefore, to make optimal use of the neuropsychological data each patient's pre- and post-operative scores were compared to create a change score. Each patient's test score were converted into a standard score using the standard deviation (SD) of the pre-operative group performance of all patients in the study. Z score was calculated as $z = (X_2-X_1)/ \mu SD_1)$, where X_1 is the pre-operative score, X_2 is the post-operative score and μSD_1 is the standard deviation of the pre-operative group scores. This technique of analysis has been adopted in a number of studies on cognitive change in cardiac surgery[14,185].

In both methods of analysis, where improved performance on any test was reflected by a lower score, as in timed tests, the direction of the score was reversed so that all improvements gave rise to a positive score and deterioration to a negative score. A global Z change score was obtained by summing the change score of the individual tests. When a participant, because of cognitive difficulties, was unable to complete a task at follow-up a score of two standard deviations below the mean of the whole group for that test was recorded.

In addition two secondary endpoints were calculated; firstly, from the mean and the SD of an individual test for the group of patients as a whole, a patient will be considered to show significant deterioration in the test if the score at an assessment falls 1 SD below the pre-operative value. A patient was judged to show an overall neuropsychological deficit if a deterioration in 2 or more of the 10 neuropsycological tests were observed, reflecting the patient's performance which is not influenced by the intrinsic ability to perform the test. Also secondly a similar assessment to that described above will be conducted except that significant deterioration will be defined as a 20% fall from the pre-operative value.

Comparison of the proportion of patients with deficit in the test and control groups was performed using the χ^2 test. Comparison of the performance of the groups on any one test was determined using the Mann Whitney U test.

Difference in microemboli count between groups were analysed using the Mann Whitney and χ^2 tests.

Each patient will act as their own control and scored against their own pre-operative performance, thereby removing patient variation in the ability to perform the tests.

5.22 Discharge from hospital

Patients were usually discharged on either day 6 or 7 following surgery, depending on their individual needs either to their homes or to their nearest hospitals for convalescence.

Details regarding timing of the patients' discharge from hospital along with their relevant clinical findings were entered into their clinical data sheets (**Appendix 8.3**).

5.23 Follow-up

All cardiac patients were routinely followed up in the outpatients' clinic 6 to 8 weeks from the time of their discharge. They were assessed clinically with an ECG and chest X-ray (**Appendix 8.3**).

5.24 Patient withdrawal

All patients recruited to the study were made aware of their right to withdraw from the study at any time without affecting their treatment or care.

5.25 Data collection, storage and analysis

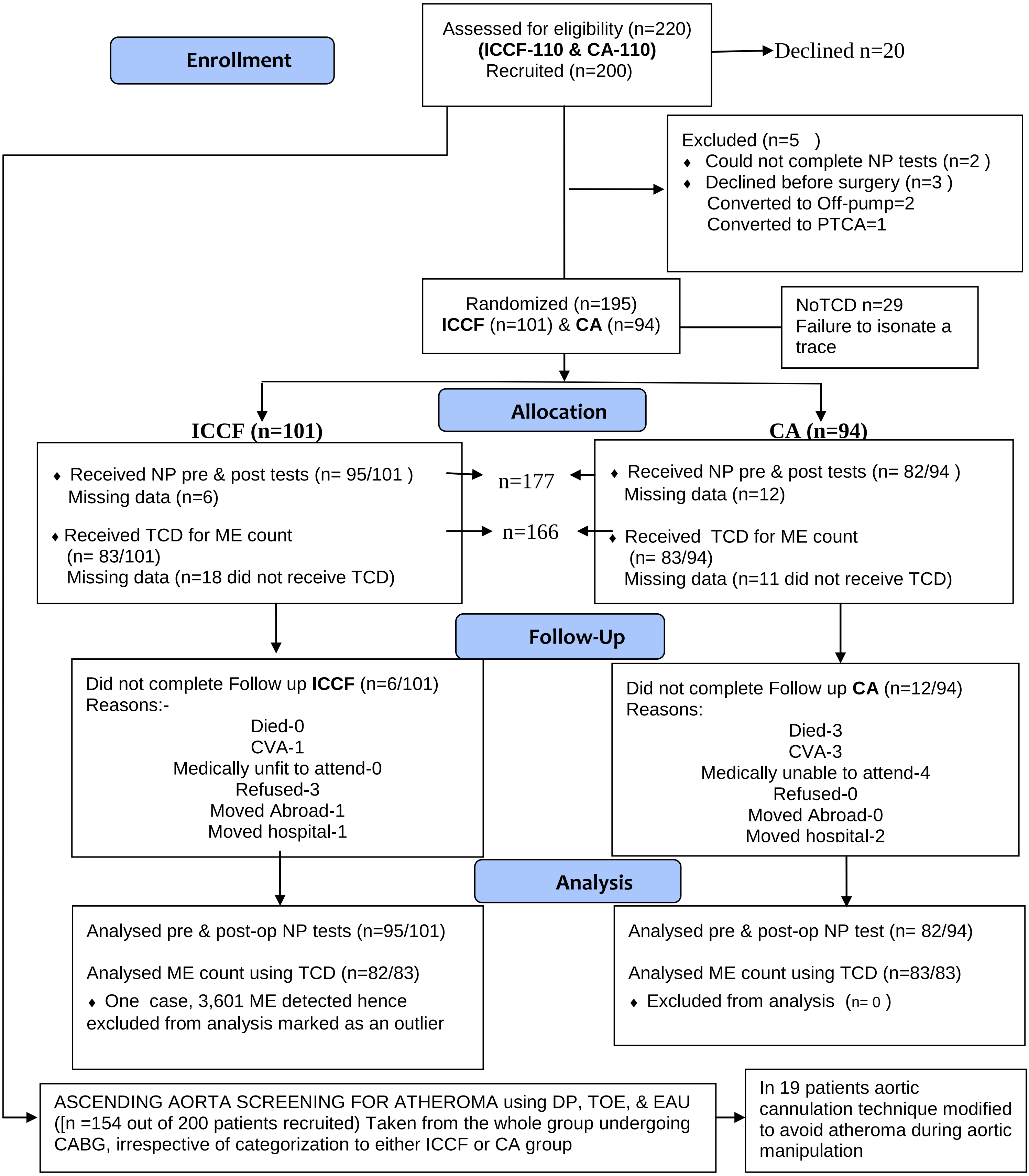
All data collected in this study by the author were stored in a hard filing cabinet according to their unique study identification serial number, thereby protecting the patient's identity according to the patient's data protection requirements.

The research fellow (J. Stygall) entered all the data for subsequent analysis, which was carried out by Mrs. Jan Stygall and the author jointly. A second investigator (Jan Stygall) reviewed 10% of the tapes to assess the inter-observer reliability.

Chapter 6

Results

CONSORT Flow Diagram: Figure 1



6. Results

6.1. Recruitment

Two hundred and twenty patients were approached and 200 agreed (n=20 declined) to participitate in the investigation between February 2002 and December 2004. Of the 200 patients recruited to the study, 5 patients (2.5%) were excluded (shown on Table 6.1) while of the 195 participants 177 (90.76%) completed both pre and post-operative NP assessments (ICCF n=95, CA n=82).

6.2. Removal from study before or during surgery

Out of 200 patients, 3 were excluded before surgery and 2 after randomization during surgery due to 2 being unable to complete NP tests, 2 scheduled for off-pump surgery and 1 for percutaneous transluminal coronary angioplasty (PTCA).

Table 6.1 Summary of reasons for removal from study after recruitment

Reason for removal	**No. of patients**
Unable to complete NP tests	2
Converted to off-pump surgery	2
Converted to PTCA	1

Therefore, 195 patients were randomized, completed pre-operative NP assessment and successfully completed theatre protocol.

6.3. Outcome after surgery

Out of 195 patients 90.76% (n=177) returned for repeat NP assessment. The reasons why 18 patients failed to return are summarized in Table 6.2.

Table 6.2 <u>Summary of reasons for not returning for NP assessment follow up.</u>

Reason for not returning for NP follow-up	**No. of patients**
Completed	177
Death	3
CVA	4
Medically unfit to return for testing (No CVA)	4
Refused to return for testing	3
Moved abroad	1
Moved hospital	3
Total	195

Table 6.3 **<u>Clinical outcomes and attendance at follow-up between groups.</u>**

Final outcome	**ICCF**	**CA**
Completed	95	82
Died	0	3
CVA	1	3
Medically unable to attend	0	4
Refused	3	0
Abroad	1	0
Moved hospital	1	2
Total	101	94

ICCF=Intermittent cross-clamp fibrillation, **CA**= Cardioplegic arrest, **CVA**=Cerebrovascular disease

There were no statistical differences found between the two groups using χ^2 tests.

Of the 3 deaths in the CA group one was due to respiratory arrest post extubation while 2 were due to multi-organ failure. There was 1 CVA in the ICCF and 3 in the CA groups, of which atheroma was detected in the ICCF as moderate and moderate and severe in 2 CA patients while no probe was available for use in the remaining patient in the CA group.

6.4. Pre-operative data

6.4.1. Patient characteristics

Of the 195 participants 181 were Caucasian, 3 Black, 7 Asian and 4 belonged to another race.

Table 6.4 Characteristics of participants (n=195)**.**

Variables	**ICCF (101)**	**CA (94)**	**p Value**
Male	89.1 %	90.4 %	
Age (yrs)	65.5 (7.7)	66.9 (8.2)	0.222
Education (yrs)	10.09 (1.7)	9.69 (1.9)	0.221
Elective	60.4 %	64.9 %	0.556
BMI (kg/m^2)	28.7 (3.7)	28.3 (4.3)	0.472
Euro Score	4.46 (2.4)	4.78 (2.3)	0.611
Ejection Fraction			
Good	74.3 %	76.6 %	
Moderate	17.8 %	18.0 %	NS
Poor	7.9 %	5.3 %	
Diabetes	14.9 %	16.0 %	0.415

Figures are expressed in means with standard deviations in parenthesis. **Yrs**=years. **BMI**= Body Mass Index.

There were no significant differences in the demographic and clinical characteristics between the two groups. The average age of the patients and predominance of male patients are in line with the UK population of patients undergoing coronary artery bypass grafting surgery (UK National Adult Cardiac Surgical Database Report 2000-2001). In the initial phase of the study Parsonnet risk stratification score was used and subsequently it was changed over to Euroscore.

6.4.2. Pre-operative cardiovascular history

Table 6.5 The pre-operative cardiovascular history of the participants (n=195).

History	**ICCF (101)**	**CA (94)**	***p Value***
Elective group	61 (60.39%)	61 (64.89%)	0.517
Stable angina	96 (95.04%)	93 (98.93%)	0.422
Unstable angina	11 (10.89%)	3 (3.19%)	0.072
MI	50 (58.41%)	47 (50%)	0.238
Dyspnoea	60 (59.40%)	57 (60.63%)	0.401
PTCA	7 (6.93%)	11 (11.70%)	0.250
Hypertensive	78 (77.22%)	76 (80.85%)	0.535
LV aneurysm	1 (0.99%)	0	0.333
Peripheral vascular disease	6 (5.94%)	7 (7.44%)	0.674
Diabetes	15 (14.85%)	15 (15.95%)	0.415
Hypercholestremia	68 (67.32%)	65 (69.14%)	0.785
Smoker Ex/Still	79 (78.21%) 58(57.42%) 21(20.79%)	66 (70.21%) 54(57.44%) 12(12.76%)	0.215

Using χ^2 there were no significant differences between the groups in pre-operative cardiovascular history

6.4.3. Pre-operative medications

The pre-operative medication regime may imitate the severity of disease and may potentially affect outcome variables such as microemboli production or the inflammatory response. Table 6.6 details the percentage of patients in the two groups using medications to control ischaemic heart disease.

Table 6.6 Number (%) of participants on pre-operative medication (n=195).

Medication	**ICCF (n=101)**	**CA (n=94)**	***p Value***
Beta Blockers	72 (71.3%)	63 (67.0%)	0.519
Nitrates	56 (55.4%)	57 (60.6%)	0.467
Ace inhibitors	51 (50.5%)	43 (45.7%)	0.507
Statins	81 (80.2%)	81 (86.2%)	0.266
Warfarin/Clopedogril*	20 (19.8%)	19 (20.2%)	0.604
Aspirin*	93 (92.1%)	88 (93.6%)	0.678
Anti-arrhythmia	3 (3.0%)	1(1.1%)	0.622

*Anti- platelets and anti-coagulants were discontinued one week prior to surgery. A small percentage of patients were on Warfarin for AF and Clopidogril post-stent insertion.

Using χ^2 there were no significant differences between the groups in pre-operative medication.

6.4.4. Pre-operative Neuropsychological tests

Table 6.7 Means and standard deviations (sd) of the raw pre-operative NP tests and mood state scores (n= 177).

NP TEST	ICCF (n=95)		Cardioplegia (n=82)	
Trail Making Test-A [a]	39.75	(12.6)	39.87	(14.9)
Trail Making Test-B [a]	85.42	(33.7)	95.28	(39.7)
Letter Cancellation Test [a]	93.50	(22.7)	98.23	(25.8)
Grooved Pegboard test D [a]	85.75	(20.9)	86.71	(20.8)
Grooved Pegboard test Non-Dominant [a]	98.52	(26.4)	96.07	(23.9)
Symbol Digital Replacement Test [a]	178.8	(49.5)	190.24	(56.3)
Non-Verbal memory Recognition test [b]	81.53	(33.95)	84.50	(24.4)
Rey Auditory Verbal Learning Test-T [c]	43.52	(9.5)	42.78	(10.1)
Rey Auditory Verbal Learning Test –Delayed [d]	-1.93	(2.1)	-2.15	(1.6)
Choice Reaction Test [b]	.57	(.16)	.57	(.12)
New Adult Reading Test [c]	33.22	(11.1)	33.06	(11.7)
Speilberger-State Trait Anxiety Inventory-S	35.97	(11.8)	37.63	(11.40)
Center for Epidemiological Studies-Depression scale	10.57	(8.1)	11.39	(8.3)

[a] Time to completion (seconds). [b] Mean response time (seconds). [c] Number correct.

[d] Difference score.

All patients received baseline pre-operative NP testing. Table 6.7 details these results. There was no significant difference using the t test in pre-operative NP scores between the two groups. The two groups were, therefore, well matched in terms of pre-operative NP performance.

6.5. Intra-operative data

6.5.1. Intra-operative clinical data

Table 6.8 Intra-operative data (n=165/166)

Variables	**ICCF(n=82)**		**CA (n=83)**		***p* Value**
Operation time	188.4	(37.3)	194.7	(29.5)	0.194
CPB time	73.4	(21.3)	72.9	(17.7)	0.891
Crossclamp time	31.3	(10.9)	41.1	(10.7)	**<0. 001**
No. Grafts	2.91		2.85		0.586
Internal mammary artery grafts	86		86		0.108
Total ME*	228.1	(352.5)	229.41	(283.2)	0.642
Post-op AF	17		16		0.890

. * Outlier excluded, one ICCF patient had 3,601 ME

Time in minutes. Standard deviations in brackets.

There were statistically significant differences noticed in the total cross-clamp time between the two groups with longer cross-clamp time in the cardioplegia group. But the overall speed of surgery when compared to other published studies does suggest that this is due to surgeons using intermittent cross-clamp fibrillation technique for myocardial protection.

No statistically significant differences were detected between the groups as shown in Table 6.8 with regard to operation time, total cardiopulmonary bypass time, number of grafts, total microemboli generation, and post operative atrial fibrillation.

6.5.2. Intra-operative mean arterial pressure

Table 6.9 Comparisons of means and standard deviations (sd) of the mean arterial pressure (MAP) between groups during pre and post bypass (n=195)

MAP	ICCF (n=101)	CA (n=94)	t-value	*p* Value
Pre-induction	77.66 (10.68)	78.63 (12.39)	-0.582	0.561
Post-induction	72.84 (13.49)	75.25 (14.50)	-1.195	0.234
Pre-sternotomy	72.83 (14.85)	76.52 (16.86)	-1.617	0.107
Post-sternotomy	8.56 (17.00)	85.51 (18.53)	-0.760	0.448
Pre-CPB	65.01 (10.45)	65.05 (10.50)	-0.029	0.977
Post-CPB	67.81 (9.40)	67.76 (10.16)	0.037	0.971
Post-skin closure	68.67 (8.94)	68.89 (9.40)	-0.167	0.867

Figures are expressed in means with standard deviations in parenthesis

No significant differences noted in the mean arterial pressure between the two groups.

6.5.3. Intra-operative temperature

Table 6.10 Comparisons of means and standard deviations (sd) of the temperature between groups during pre and post-bypass periods (n=195)

Temperature	ICCF (n=101)	CA (n=94)	t-value	*p* Value
Pre-induction	36.46 (.31)	36.45 (.34)	0.170	0.865
Post-induction	36.06 (.41)	36.04 (.38)	0.341	0.734
Pre-sternotomy	35.70 (.42)	35.58 (.48)	1.857	0.065
Post-sternotomy	35.54 (.455)	35.35 (.53)	2.726	**0.007**
Pre-CPB	35.09 (.58)	34.88 (.54)	2.627	**0.009**
Post-CPB	36.92 (.47)	36.86 (.65)	0.704	0.482
Post-skin closure	35.82 (.51)	35.82 (.53)	0.000	1.000
Min temp during operation	31.95 (.60)	31.78 (.34)	2.481	0.014
Max temp during operation	37.33 (.22)	37.39 (.25)	-1.974	0.050
Rewarming time	17.07 (4.0)	18.22 (4.43)	-1.883	0.061

Figures are expressed in means with standard deviations in parenthesis.

The Post sternotomy and pre bypass temperature in the cardioplegia group was found to be significantly cooler when compared with the intermittent cross clamp fibrillation group.

6.5.4. Intra-operative screening of the ascending aorta

6.5.4.1. Patient characteristics and co-morbidities

The characteristics of the 154/195 patients (78.97%, n=154/195) who underwent assessment of their ascending aorta using DP, TOE and EAU are shown in Table 6.11.

Table 6.11 Patient characteristics and co-morbidities

Variable	**Value**
Age	66 ± 8.03
Male	142 (92%)
Female	12 (8%)
Ejection fraction	
Good	118 (77%)
Moderate	26 (17%)
Poor	10 (6%)
Insulin dependent diabetes mellitus	13 (8.4%)
Non-insulin dependent diabetes mellitus	7 (4.5%)
Diet-controlled diabetes mellitus	3 (1.9%)
Hypercholestremia	112 (72.7%)
Hypertension	124 (80.5%)
Pre-operative statin use	130 (84.4%)
Peripheral vascular disease	11 (7.1%)
Body mass index	28.30 ± 3.75
EuroSCORE	5.21 ± 6.3

Values are number of patients (percentage) or mean ± S

6.5.4.2. Digital palpation (DP) comparing Epiaortic ultrasonography (EAU)

Table 6.12 Comparing detection of atheroma by DP and EAU

	DP			
	Atheroma	Present	Absent	Total
	Present	17	64	81
EAU	Absent	3	70	73
	Total	20	134	154

Sensitivity and specificity of DP in detecting aortic atheroma against EAU (gold standard)

Sensitivity **[Σ +ves] = Σ + ves ÷ Σ + ves + Σ + false × % = 20.98%**

[17 ÷ 17 + 64 × 100 = 20.98 %]

Specificity **[Σ -ves]= Σ -ves ÷ Σ - ves + Σ + false × % = 95.89 %**

[70÷70+3×100=95.89%]

6.5.4.3. Transoesophageal echocardiography (TOE) comparing Epiaortic ultrasonography (EAU)

Table 6.13 Comparing detection of atheroma by TOE and EAU

	TOE			
EAU	Atheroma	Present	Absent	Total
	Present	**25**	56	81
	Absent	6	**67**	73
	Total	31	123	154

Sensitivity & specificity of TOE in detecting aortic atheroma against EAU (gold standard)

Sensitivity **[Σ +ves] = Σ + ves ÷ Σ + ves + Σ + false × % = 30.86 %**

[25 ÷ 25 + 56 × 100 = 30.86 %**]**

Specificity **[Σ -ves]**= **Σ -ves ÷ Σ - ves + Σ + false × % = 91.78 %**

[67÷67+6×100=91.78%**]**

6.5.4.4. Transoesophageal echocardiography (TOE) comparing epiaortic ultrasonography (EAU) of proximal ascending aorta

Of the 47 patients identified as having atheroma in the proximal segment of the ascending aorta by EAU, 26 (55%) of these were not detected by TOE. Of the 31 patients identified as having atheroma using TOE, 10 (32%) of these patients showed a normal proximal aorta with EAU (Table 6.14).

Table 6.14 Comparing detection of atheroma by TOE and EAU proximal-epiaortic ultrasonography

	TOE			
	Atheroma	Present	Absent	Total
EAU proximal	Present	**21**	26	47
	Absent	10	**97**	107
	Total	31	123	154

Sensitivity **[Σ +ves] = Σ + ves ÷ Σ + ves + Σ + false × % = 44.68 %**

[21 ÷ 21 + 26 × 100 = 44.68 % **]**

Specificity **[Σ -ves]**= **Σ -ves ÷ Σ - ves + Σ + false × % = 90.65 %**

[97 ÷ 97 + 10 × 100 = 90.65

6.5.4.5. Comparing all Digital palpation, Transoesophageal echocardiography and Epiaortic ultrasonography (proximal, middle & distal ascending segment)

Table 6.15 Comparing detection of atheroma by DP, TOE and EAU.

Atheroma	**Present**	**Absent**
DP	20	134
TOE	31	123
EAU	81	73

6.5.4.6. EAU detection of atheroma in the proximal, middle & distal ascending segment

The extent of overlap between detection of atheroma at the mid and proximal sites of the ascending aorta by EAU indicated that in 24 (36%) of the 67 cases where atheroma was found in the mid-segment it was not detected in the proximal segment. In contrast, in 92% of cases (43/47) where atheroma was detected at the proximal segment it was also found in the mid-segment of the ascending aorta. A comparison between the proximal and distal sites showed 43% (23/53) instances of distal atheroma not detected proximally and 36% (17/47) cases of proximal atheroma not found to have atheroma distally (Table 6.16).

Table 6.16 Presence or absence of atheroma in the proximal, middle & distal segment of the ascending aorta as detected by EAU.

	EAU middle			
	Atheroma	**Present**	**Absent**	**Total**
EAU proximal	**Present**	**43**	**4**	**47**
	Absent	**24**	**83**	**107**
	Total	**67**	**87**	**154**

	EAU distal			
	Atheroma	**Present**	**Absent**	**Total**
EAU proximal	**Present**	**30**	**17**	**47**
	Absent	**23**	**84**	**107**
	Total	**53**	**101**	**154**

6.5.4.7. Total atheroma detection by DP, TOE & EAU

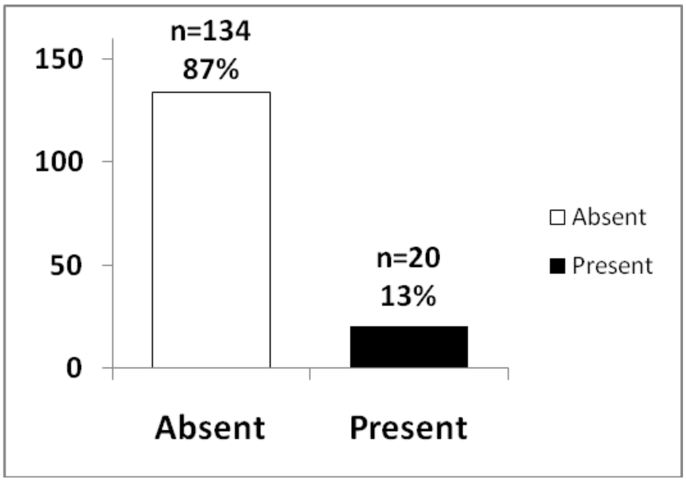


Figure 2. Total atheroma detected by DP n=20

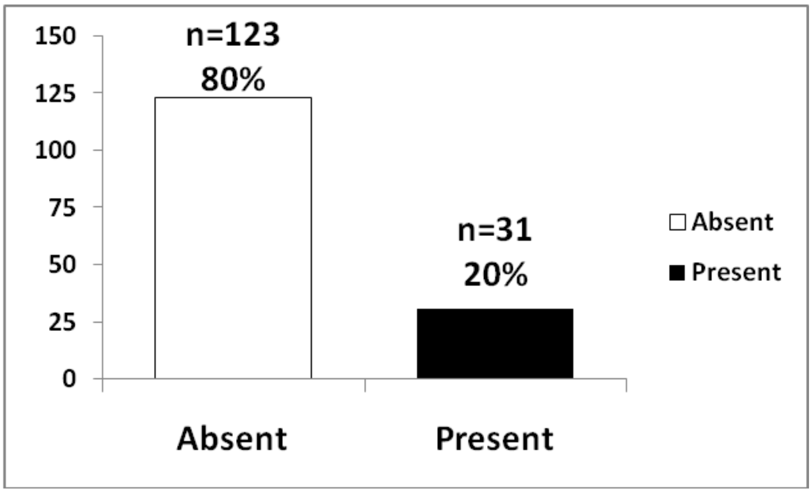


Figure 3. Total atheroma detected by TOE n=31

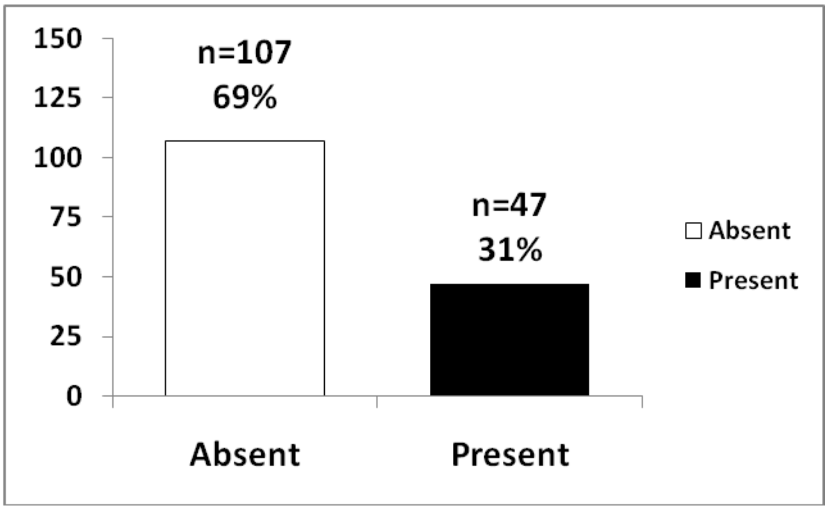


Figure 4. Total atheroma detected by EAU n=47,

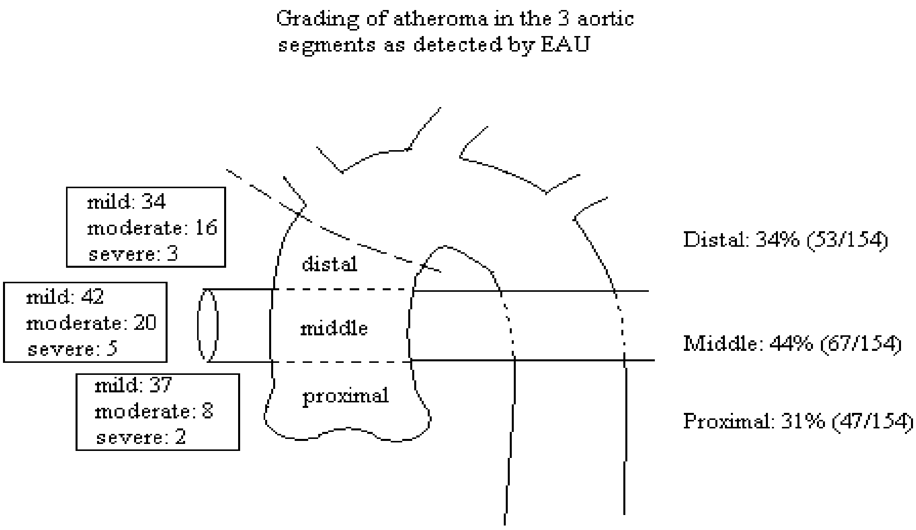


Figure 5. Grading of atheroma of three segments detected by EAU n=167 in 81 patients

6.5.4.8. Grade score of atheroma

The proportions of mild, moderate and severe atheroma in each segment of the ascending aorta using EAU are summarized below in Table 6.17. Atheroma was most common in the mid-segment of the ascending aorta (67/154; 44%), followed by the distal (53/154; 34%); with the least atheroma detected in the proximal segment (47 /154, 31%).

Table 6.17

Frequency of mild, moderate and severe atheroma in the three aortic segments (proximal, middle & distal) as detected by EAU in the 81 patients:

Grading and distribution of atheroma in the 3 segments of the 81 patients detected by EAU technique.

	Proximal	**Middle**	**Distal**	**Total**
Mild	37	42	34	113
Moderate	8	20	16	44
Severe	2	5	3	10
Total	47	67	53	167

6.5.4.8. Atheroma grading as detected by DP, TOE and EAU in the four patients with cerebrovascular accident (CVA)

In 3 patients atheroma was scored as present using DP while in 2 of them TOE graded atheroma as mild while EAU graded proximal, mid and distal segment as moderate and severe. In the third patient, TOE and EAU graded atheroma as normal. In the fourth patient EAU detected mild atheroma in all the three segments while DP and TOE were normal.

Table 6.18:

Pt with CVA	DP	TOE	EAU-proximal	EAU-mid	EAU-distal
1	Present	Mild	Moderate	Moderate	Moderate
2	Present	Mild	Severe	Severe	Severe
3	Absent	Normal	Mild	Mild	Mild
4	Present	Normal	Normal	Normal	Normal

6.5.4.10 Intra-operative transcranial Doppler (TCD) data of microemboli (ME)

One hundred and sixty-six patients (85.12%) out of 195 patients had complete intra-operative TCD monitoring of the right middle cerebral artery along with video recording on to a VHS tape. Microembolic events were counted throughout from cannulation to 15 minutes post-decannulation.

Table 6.19 Medians and range of ME detected at different surgical time-points. Comparison by Mann-Whitney test (n=165/166).

Surgical event	ICCF (n=82)	CA (n=83)	Z	p Value
Cannulation	2 (0 – 12)	2 (0 – 15)	-0.483	0.629
Icpb	7 (0 – 110)	8 (0 -71)	-1.551	0.121
x-clamp on	3 (0 – 75)	5 (0 – 83)	-0.645	0.519
x-clamp off	1 (0 – 68)	0 (0 - 21)	-2.151	0.031
PA on	2 (0 -60)	2 (0 – 125)	-0.051	0.959
PA off	3 (0 – 34)	4 (0 – 56)	-1.141	0.254
cCPB	0 (0 – 5)	0 (0 – 5)	-0.005	0.996
Decannulation	0 (0 – 6)	0 (0 – 8)	-1.721	0.085
15 mins post	0 (0 – 6)	0 (0 – 19)	-1.895	0.058
Spontaneous	71 (6 – 1525)	68 (0 – 1,176)	-0.443	0.658
Total ME*	105 (9 – 1757)	110 (1 – 1,306)	-0.579	0.563

* Outlier excluded iCPB = initiation of CPB, x-clamp on = cross-clamp on, x-clamp off = cross-clamp off, PA on = proximal anastomosis on, PA off = proximal anastomosis off, cCPB = cessation of CPB, 15 mins post = during the 15 minutes post cannulation.

The total number of ME detected per participant from cannulation to 15 minutes post-decannulation ranged from 1 to 1757 (mean=231.01, sd=318.9) and a median of 107 (inter-rater reliability r=.91). In one participant, 3,601 ME were detected (ICCF group). Therefore, all the analyses involving ME were conducted both with and without this outlier. No differences between these analyses were found.

There was no significant difference (Mann-Whitney Test) in total emboli count between the two groups or ME occurring at any of the different stages of the operation including periods of no manipulation.

6.6. Post-operative data

6.6.1. Post-operative clinical data prior to discharge

Table 6.20 Number (%) of participants with post-operative complications prior to discharge (n=195).

Complications	**ICCF (n=101)**		**CA (n=94)**		***p Value***
IABP	1	(0.99%)	2	(2.15%)	0.513
Inotropes	21	(20.79%)	12	(12.76%)	0.135
ECG-AF	11	(10.89%)	8	(8.69%)	0.568
Post MI	1	(0.99%)	0		0.341
Bleeding	4	(3.96%)	4	(4.39%)	0.880
Cardiac arrest	2	(1.98%)	1	(1.09%)	0.623
Low cardiac output	10	(9.90%)	13	(14.28%)	0.350
CVA	1	(0.99%)	3	(2.15%)	0.513
Psychosis	2	(1.98%)	4	(4.39)	0.337
Multi-system failure	1	(0.99%)	2	(2.19%)	0.500
Respiratory failure	1	(0.99%)	2	(2.19%)	0.500
Renal-filtration	1	(0.99%)	3	(3.29%)	0.264
Operative death	0		1	(1.08%)	0.293
Post-op death	0		2	(2.1%)	0.134
Days to discharge	7		8		0.198

Using χ^2 there were no significant differences between the groups in post-operative complications prior to discharge

6.6.2. Out-patients follow-up data

In the outpatients' clinic 177 patients (90.76%) out of 195 were followed up while 18 patients (9.2%) were missing as mentioned earlier (Table: 6.2).

No significant differences were noted between groups with reference to recurrence of angina, shortness of breath, sternal, leg and forearm wound healing, readmission to hospital, drug usage (aspirin, ace-inhibitor, statins, warfarin, clopidogril, beta blockers).

6.6.3. Post-operative NP data

In total, 90.76% (n=177, ICCF n=95 & CA n=82) out of 195 participants underwent complete pre and post-operative NP testing.

6.6.4. Post-operative 6-8 week Mean Z change score

Table 6.21 Comparisons (n=177) of means and standard deviations (SD) of Z change score for all NP tests at 6 weeks post-surgery in the intermittent cross-clamp fibrillation (ICCF) and cardioplegia (CA) group.

Table 6.21 (n=177)

TEST	ICCF (n=95)	CA (n=82)	t-value	*p* Value
Trail Making Test-A [a]	0.183 (0.94)	0.093 (0.79)	0.677	0.499
Trail Making Test-B [a]	-0.029 (0.71)	0.167 (0.72)	-1.813	0.072
Letter Cancellation Test [a]	0.300 (0.82)	0.288 (0.75)	0.102	0.919
Grooved Pegboard Dominant [a]	0.535 (0.68)	0.554 (0.62)	-0.185	0.854
Grooved Pegboard Non-Dominant [a]	0.621 (0.64)	0.443 (0.56)	1.956	0.052
Symbol Digital Replacement Test [a]	-0.044 (0.68)	0.215 (0.67)	-2.521	0.013
Non-Verbal Recognition Memory Test [b]	0.100 (0.68)	0.194 (0.64)	-0.937	0.350
Rey Auditory Verbal Learning Test-T [c]	-0.128 (0.73)	0.080 (0.79)	-1.815	0.071
Rey Auditory Verbal Learning Test –Delayed [d]	0.128 (1.3)	0.100 (1.4)	0.134	0.893
Choice Reaction Test [b]	0.025 (0.64)	-0.076 (0.89)	0.870	0.386
Total NP change*	1.69 (3.31)	2.06 (3.4)	-0.720	0.473

Figures are expressed in means with standard deviations in parenthesis. [a] Time to completion (seconds). [b] Mean response time (seconds). [c] Number correct. [d] Difference score.* This score was calculated with Choice Reaction Time included. When analysed with this test excluded, the difference between the two groups remained non-significant (*P=0*.326).

6.6.5 Comparison of characteristics of patients followed up and withdrawn

The follow-up rate was 90.76 % for the 6-week repeat NP testing. The pre-operative and intra-operative findings were compared between patients who did and did not return for follow-up. The idea was to analyse all the patients who failed to return for whatever reason so that the 3 patients who died were included in the 18 patients withdrawn (Table 6.22).

Table 6.22 Peri-operative characteristics of patients followed up or withdrawn (n=195).

Variable	**Returned** (n=177)	**Withdrawn** (n=18)	***p Value***
Age	65.85(7.720)	69.67(9.792)	0.053
Sex Male Female	161 16	14 4	0.079
Years of Education	9.92(2.010)	9.75(3.019)	0.793
BMI	28.59(3.900)	27.64(4.977)	0.356
Ejection fraction Good Moderate Poor	 133 32 12	 14 3 1	 0.966
Euroscore Score	4.49(2.244)	6.06(2.980)	**0.007**
Speilberger State (anxiety)	36.77(11.792)	37.00(8.874)	0.346
CESD (depression)	10.84(8.162)	13.25(8.648)	0.662

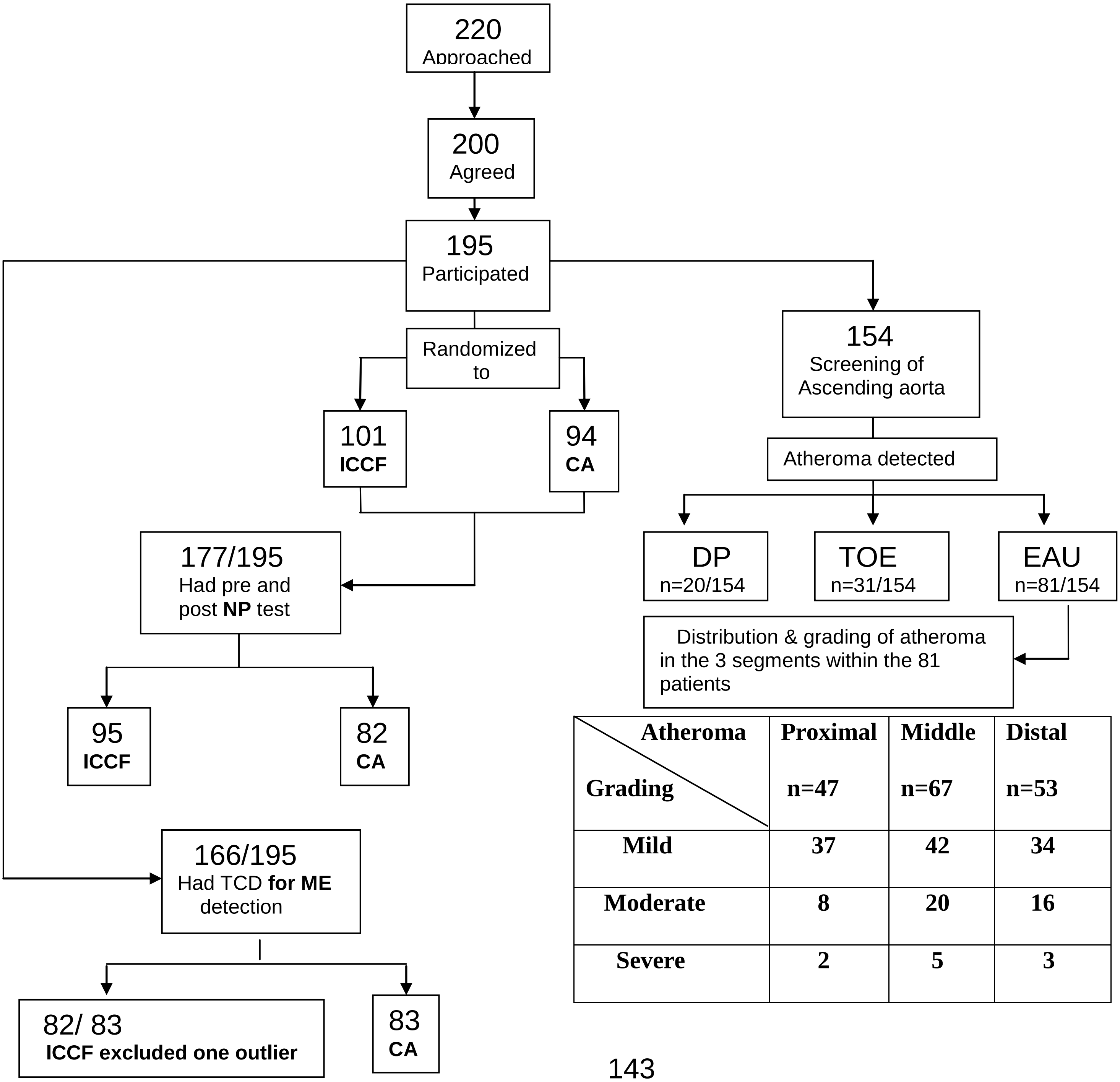
The only significant difference was found in the Euroscore (p = .007) with those not completing having a significantly higher Euroscore (mean 6.06) than those completing (mean 4.49).

6.6.5. Relationship of ME to NP outcome

A total of 166 patients received intra-operative TCD and also completed NP follow-up at 6-8 weeks.

6.7. Summary

Figure 6: Summary of number of patients receiving the main tests



Grading \ Atheroma	Proximal n=47	Middle n=67	Distal n=53
Mild	37	42	34
Moderate	8	20	16
Severe	2	5	3

Chapter 7

Discussion of results

7. Discussion of results

7.1. Introduction

The study of neuropsychological (NP) outcomes following coronary artery bypass grafting (CABG) surgery has been challenging for a number of reasons. Since it was performed, there have been ongoing improvements in surgical and anaesthetic techniques, as well as changes in the patient population undergoing CABG. The surgical population not only is older, but has greater prevalence of associated disease, particularly diseases that are known risk factors for cerebrovascular disease. As a consequence, the investigations and NP outcomes after CABG surgery in many ways has been a study of a moving target. All these may or may not add to mortality, days in hospital and the use of rehabilitation facilities[223].

This study presented in this thesis evolved from one small study comparing the post-operative neuropsychological (NP) performance and microemboli (ME) generation in patients undergoing intermittent cross-clamp fibrillation(ICCF) or cardioplegic arrest (CA) during CABG finding no significant differences between the two groups[10]. However with only 70 participants being followed up at 6 months the study was underpowered.It excluded patients with aortic disease which may have reduced the impact of repeated cross-clamping.Also; flow rates and body temperatures differed between the groups, leaving the possibility that other risk factors could have confounded the results.

Therefore this randomized study set out to compare the generation of microemboli and post-operative neuropsychological performance outcomes as the primary objective while comparing the detection of atheroma in the ascending aorta using three intra-operative screening techniques Digital palpation (DP), Transoesophageal echocardiography (TOE) and Epiaortic ultrasonography (EAU) in a large group undergoing either intermittent cross-clamp fibrillation (ICCF) or cardioplegic arrest (CA) during coronary artery bypass grafting (CABG) surgery.

7.2.Microemboli generation comparing the two myocardial protection techniques

As previously discussed, the relationship between ME generation and NP outcome is complex. Although ME are considered to be an important mechanism in the aetiology of NP changes post-CABG, it is well accepted that this is a multifactorial problem and the changes are not attributable to ME alone.The generation of ME during manipulation of the aorta has been often cited as a cause for concern when considering ICCF as a technique for myocardial protection.

Most investigators have continued to use TCD as the current method for detecting intra-operative ME despite its limitations. Only 90 % of the people have an adequate window in the temporal bone through which the middle cerebral artery can be isonated.This anatomical and technical problems (as explained in the results chapter, the video recorder failed to record a trace for 29 patients = 14.87%) with trace recording meant that not all (166/195 =85.12%) patients in the present study received TCD monitoring. The right cerebral artery is one of the six arteries supplying the circle of Willes leading to the question if one or both middle cerebral artery should be isonated.Some studies have shown that a combined count of both the middle cerebral artery recording is more accurate as it is closer to the total number of ME.However this is likely to be just a proportionate estimate unless all the six arteries are monitored. Moser et al [162] study suggests that it does not matter whether the unilateral or bilateral/ right or left middle cerebral artery is used for monitoring.Wijman et al [157] have shown that cerebral ME occurs frequently in the middle cerebral artery when compared to the anterior cerebral artery using TCD.Another limitation of the TCD is its inability to differentiate gaseous from particulate ME, let alone the many types of particulate microemboli have been addressed in the previous chapters. Future study should have the potential to determine which factors carry pathogenic influence.

As with most TCD studies ME were found in all participants and the number of ME detected was comparable to Arrowsmith et al and Stroobant et al[14,15] studies showing no difference between groups.

There was, however, no correlation between NP changes scores and number of ME.In this study Spearman's rho correlations were conducted between total ME and NP change scores, revealing no correlations either as a whole group (rho = 0.159) or separately by group (ICCF:rho = 0.063, p =0.581 versus CA: rho = 0.244, p =0.036). It is important, however, that a relationship between NP performance and ME is not always found given the limitations of microemboli detection as it is unsurprising to find no consensus in the literature. Although some studies (Bonchek et al 2003[102], Brown et al 2000[63], Stump et al 1996[11] and Barbut et al 1994[99]) have found a relationship, other investigators (Arrowsmith et al 1998[14] and Stroobant et al 2005[15] and) have not found any. One explanation for this may relate to the composition of the ME. It is probable that particulate matter may lead to a greater impact on the brain in comparison to gaseous ME because the gaseous bubble may dissolve as the partial pressure changes while particulates will form a complex block across the capillaries. The composition of ME can be either particulate (atheroma, fat, platelet aggregates, foreign material from the equipment used etc) or air. The final location where the ME lodges in the brain cannot be determined and the area may not be covered by the cognitive tests that are currently used.

The use of ICCF remains to be popular among certain units in the UK because of recent evidence that it may produce an ischaemic pre-conditioning effect on the heart[217] . Most studies in literature have used cardioplegic myocardial protection techniques, which tend to be associated with a longer bypass and ischaemic times. The relative short bypass times with intermittent cross-clamp techniques would be expected to decrease ME count on the assumption that the relationship is linear. Although repeated cross-clamping of the ascending aorta can theoretically increase ME production there is no consistent evidence that intermittent cross-clamp fibrillation produces more ME than cardioplegic techniques as shown by Musumeci[10] et al in 1998. In fact it is possible that since ICCF tends to be associated with shorter cross-clamp and bypass times, the total ME generated could be less than with cardioplegia. Musumeci study, however, failed to show any significant differences in the number of peri-operative ME generated or post-operative NP outcome. However, with only 70 participants completing the follow-up assessment at 6 months, the study was underpowered to detect any significant changes in NP performance. In addition the exclusion criteria in this study of patients with aortic disease may have reduced the impact of repeated cross clamping. Finally, both flow rates and body temperature differed in the two groups leaving the possibility that factors other than differences in myocardial protection could have perplexed the results.

There are some important differences between the present study described in this thesis compared to Musumeci and collegues [10] study mentioned above: the participants in our study were older and none were excluded if they had aortic disease; also, body temperature and flow rate during CPB did not differ between the two groups.Both groups were well matched in terms of pre-operative characteristics, but ischaemic time was shorter in the intermittent cross-clamp fibrillation group with a significantly longer ischaemic time in the cardioplegia group ($p < 0.001$).No differences in operation time,CPB time,total number of grafts,or internal mammary artery grafts.There were no difference between groups in the number of patients developing post-operative atrial fibrillation (Table 6.8). Epiaortic ultrasonography and transoesophageal echocardiography resulted in the site of aortic cannulation being changed in 18 patients to avoid atheroma. In all the right cerebral artery was isonated and its recording obtained in 166 patients (n =166/195, 85.12%).

Shorter cross-clamp times have frequently been found in patients undergoing intermittent cross-clamp fibrillation, compared to those receiving cardioplegia but this has not been noted in all studies[104-105,108] . It has often been debated whether a shorter CPB time with intermittent cross-clamp fibrillation may be better for the brain when compared to cardioplegic arrest [10,105]. No CPB time difference was found in this study, possibly because all surgeons were skilled in both techniques, resulting in short bypass times (mean <74 minutes) in both groups.

A number of studies have demonstrated that the occurrence of ME can be linked to various aspects of surgery. In particular they have been related to the onset of bypass, aortic cannulation and removal of clamps[11] . Given the difference in the 2 procedures it is likely that the number of microemboli generated at each manoeuvre may vary between the 2 groups. In this study even though a greater number of ME were detected in the ICCF group at the removal of cross-clamp, this difference was not significant. However, during all of the other 8 manipulations, the number of ME was higher (albeit not significantly) in the cardioplegia group. As with previous studies[11,15] although showers of ME were detected at the time of the 9 surgical events, especially initiation of CPB and proximal anastomosis, the majority of ME occurred spontaneously. In this study, the number of spontaneous ME constituted approximately 80% of the ME in each group, resulting in no difference being found between the groups in total ME. These findings differ from Musumeci et al[10] who found that patients undergoing ICCF produced more ME during surgical manipulation whereas with CA the majority of the emboli occurred spontaneously. This difference may be due to methodological factors regarding ME detection and the criteria for considering the ME as related to a surgical event. We rated ME as being associated with a surgical event if they occurred within 1 minute of a manoeuvre, a definition used previously by other authors[11,12,99]; however, the time-frame used was not stated in the Musumeci et al paper[10]. It is of note that no differences were found between the 2 groups in the occurrence of ME at each surgical event, despite the increased manipulations of the aorta in ICCF.

7.3. Neuropsychological outcome

A substantial number of investigations have endeavoured to clarify the causes of post-operative NP deficits, yet the cause and mechanisms of NP dysfunction remains unconfirmed. This study has established that there is no evidence for any difference in the generation of ME and the NP changes produced between ICCF and cardioplegia methods of myocardial protection at each surgical event, despite increased manipulation of aorta in the fibrillation group. Both the groups showed an overall improvement in NP performance post-operatively.

This study confirms similar findings as shown by Musumeci and colleagues[10], where the Luria Nebraska Neuropsychological Battery of tests comparable to the Wechsler Adult Intelligence Test-Revised was used (WAIS-R). These tests were carefully chosen to be sensitive to detect change and thus compliant to repeated administration. One measure of cerebral damage is the inability to learn a task or strategy, which is the underlying basis of practice effects. The form of analysis used in this study takes into account any learning, or failure to learn post-operatively, and a general improvement would be expected. The NP tests were performed with an established and widely used battery and produced no significant differences between the groups in overall performance or any of the individual tests.

As the overall neuropsychological change score was considered as the primary end-point of the study, the findings should be considered to suggest that using neuropsychological change, as an index of the potential impact of these two procedures on brain function, is equivalent at least under the conditions and testing procedures performed here.

It has been argued that mood prior to cardiac surgery, especially anxiety, may influence NP performance[10,226,232]. However, the groups were well matched through random allocation on mood and more importantly no association between NP performance and anxiety and depression was seen. Therefore, the lack of differences seen in overall NP performance was not related to mood. Both groups showed an overall improvement in NP performance post-operatively, learning which is what you would expect.

Finally, most interestingly comparisons were made of patient characteristics, baseline NP performance and baseline mood state between those attending the follow-up NP assessment and those not attending. The only significant difference was found in the Euroscore (p=.007) with those not completing having a significantly higher Euroscore (mean 6.06) than those completing (mean 4.49).There were no significant preoperative differences between the groups in demographic characteristics, premorbid intelligence quotient, neuropsychological or mood status (Tables 6.4 and 6.7). There was no correlation between anxiety (r = 0.135, p = 0.122) or depression (r = 0.032, p = 0.717) and neuropsychological performance outcome.

7.4. Screening of the ascending aorta using three different techniques for atheroma

As previously mentioned Kapetanakis et al[108] in a risk-adjusted study of 7,272 patients undergoing CABG showed that the incidence of post-operative cerebral injury increases with aortic manipulation. Therefore, detection of atheroma in the ascending aorta prior to manipulation during CABG is considered to be important to reduce the overall incidence of cerebral injury and NP deficit[178,216] . Various investigators have examined the usefulness of DP, TOE and EAU in the past[127,128,129]. Despite this, EAU is not *routinely* used in cardiac surgery. Davila-Roman[113] and Royse[130] have demonstrated the superiority of EAU over TOE and DP to detect atheroma in all age groups.

This study compared the relationship between the findings of DP, TOE and EAU in the detection of atheroma in the ascending aorta. A total of 154 patients had their ascending aorta screened using all the three screening techniques. Using DP, atheroma was detected in 20 patients (13 %), using TOE in 31 patients (20%) and using EAU in 81 patients (53%).

Assuming that EAU is the 'gold standard', TOE and DP were compared with EAU to assess the relative sensitivity and specificity of each for atheroma detection. When DP was compared with EAU, 17 of the 20 cases identified by DP were positively identified by EAU (Table 6.12**).** Therefore, this shows that DP has a poor sensitivity for the detection of aortic atheroma with only 20% of the atheroma found using EAU being detected. This may be due to the fact that the finger can easily miss lesions within the lumen and is only suited to detecting the much larger, calcified lesions. Although the specificity of DP against EAU is relatively high, there were 3 false positives, which further demonstrate the relative lack of accuracy of DP compared to EAU. These findings were similar to 2 other previous studies; Royse et al study of 70 patients, who found that DP was an insensitive method for detecting atheroma, as 50% of important atheroma detected by EAU was not found on DP[130]. Bolitin et al (n=105) also found DP to detect 55% (n=22/40) of atheroma found on EAU[128].

Comparing TOE with EAU, 25 of the 31 cases graded as positive for atheroma by TOE were positive for atheroma with EAU. In 6 cases, atheroma was detected with TOE but EAU detected no atheroma (Table 6.13). These 6 false positives may be due to artefacts generated in the near field of the plane of ultrasound. Furthermore, clear visualization of the distal ascending aorta may be difficult due to the trachea and left main bronchus lying between the oesophagus and aorta as highlighted in the earlier chapter[124]. Therefore, due to difficulties in visualizing the ascending aorta clearly beyond the proximal segment of the ascending aorta using TOE it could be argued that the most appropriate comparison of the capabilities of these two techniques in imaging atheroma should be to compare TOE detection with EAU detection in the proximal segment of the ascending aorta. Of the 47 patients identified as having atheroma in the proximal segment of the ascending aorta by EAU, 26 (55%) of these were not detected by TOE. Of the 31 patients identified as having atheroma-using TOE, 10 (32%) of these patients showed a normal proximal aorta with EAU (Table 6.14). Since there were difficulties in visualising the mid and distal ascending aorta using TOE when comparing TOE with the EAU proximal findings. TOE detected only 45% (21/47) of the cases found to have atheroma in the proximal segment of the aorta compared to EAU. These findings suggest that even where it is purported to have the best imaging ability TOE does not detect as many cases with atheroma as EAU. The relative sensitivities of TOE and DP for detecting atheroma in the ascending aorta were low at 30.86% and 20.98% in comparison to EAU (Tables 6.12 & 6.13). Despite these imaging difficulties, TOE has been recommended as a screening technique and has been shown to improve outcomes in CABG[117,125].

The EAU findings were used to describe the distribution of atheroma in the ascending aorta (Table 6.15). Atheroma was most common in the mid-segment of the ascending aorta (67/154; 44%), followed by the distal (53/154; 34%); with the least atheroma detected in the proximal segment (47 /154, 31%).

The extent of overlap between the detection of atheroma at the mid and proximal sites of the ascending aorta by EAU indicated that in 24 (36%) of the 67 cases where atheroma was found in the mid-segment, it was not detected in the proximal segment. In contrast, in 92% of cases (43/47) where atheroma was detected at the proximal segment it was also found in the mid-segment of the ascending aorta. A comparison between the proximal and distal sites showed 43% (23/53) instances of distal atheroma were not detected proximally and 36% (17/47) cases of proximal atheroma were not found to have atheroma distally (Table 6.16).

Therefore, this study shows that when examined by EAU, the mid-segment of the ascending aorta yielded the greatest incidence of atheroma, followed by the distal and finally the proximal segment. These findings were similar to Sylivris et al[122] study involving 100 patients in whom EAU was found to be superior to both TOE and DP in all three segments, especially so in the mid and distal segment. These findings are important since aortic cannulation, application of cardioplegia line, cross clamping of aorta and application of side-clamp for top-end anastomosis is usually conducted in the middle and distal segment of the ascending aorta. It is only with an assessment of all segments of the ascending aorta that atheroma will be detected. The ability to generalize to other segments of the ascending aorta, based on findings from the proximal segment of the ascending aorta in particular, is poor. This further strengthens the argument for imaging the ascending aorta using EAU instead of just using a TOE imaging modality.

Since previous investigators have associated the presence of severe atheroma with higher incidence of cerebral injury[115,117,118], grading and location of atheroma are important in predicting the overall clinical outcome. Using EAU in this study atheroma detected in the proximal segment showed mild 72%, moderate 12% and severe 4%; middle segment showed mild 62%, moderate 29% and severe 7% and distal segment showed mild 64%, moderate 30% and severe 5% (Table 6.17). In this study, 4 patients had CVA. Using TOE and EAU, in 3 patients the atheroma was graded as mild, moderate and severe while the fourth was graded as normal (Table 6.18). Therefore, in summary in this study of elective patients undergoing CABG, the atheroma was detected in 53% by EAU. Furthermore, in 19 (24%) of these patients, surgical technique was modified to avoid sites of atheroma during aortic manipulation. These findings suggest that currently the detection of atheroma by EAU should be considered as a routine procedure in CABG so that any neurological incidence could be minimized.

We have used definitions of important atheroma that would result in including more lesions. And perhaps as expected, the EAU seems to be more sensitive to detecting these plaques. High frequency probes applied directly to the aorta would be expected to detect smaller lesions.

7.5.Summary

This studies finding therefore suggest that there are no overall differences in microemboli generation between ICCF and CA the two common methods of myocardial protection, and that these techniques do not result in different degrees of neuropsychological outcome.

7.6. Strengths and weaknesses of the study

Before drawing some conclusions it is worth commenting on the strengths and weaknesses of the study and discussing how this should limit interpretation.

A prospective randomized trial is the most scientifically valid of various types of clinical study. However, such clinical trials have inherent limitations because however rigorous the attempts are to standardize procedure, there will be events and variables beyond the investigators' control. For example, although we devised a standard protocol for screening the ascending aorta, it was not possible to screen all randomized trial patients using the 3 screening techniques because of unavailability of echo probes as other patients by other clinicians were using them. There were limitations to the extent one can impose protocols on clinicians however willing they are to participate in trials. Randomization should deal with the uncontrollable variables if numbers are adequate and this has been the case in the present study.

At present unfortunately, there is no one single gold-standard NP test battery for measuring

NP outcome and no universal scoring method exits as noted by a study reviewing 62 clinical studies were less than half of the studies included the tests as recommended by the 1995 consensus statement[227]. All the NP tests used in this study have been widely used and are in agreement with the recommended consensus statement for assessing NP changes following cardiac surgery[83]. Although there are a number of approaches to assess NP changes following CPB surgery, in most cardiac surgical situations patients are under tight time constraints in receiving investigations and prepation for surgery. This often limits the time available for NP testing. This in reality limits the testing time to approximately one hour. During which time studies have to be limited, naturally with more number of tests used it might be possible to detect more deficits.

In particular, the binary classification fails to account for the frequently observed improvements that occur with repiation on NP tests because it considers only deterioration in performance while the improvements observed in the tests are considered as an unwanted occurrence. Therefore, this classification suffers from a number of issues regarding its sensitivity and the fact that it is conventionally defined and these 2 factors limit its ability[218,219]. The alternative method is to use a continuous measure of performance. Here the standardized Z score used in this study has been widely utilized in other studies[193]. In this study, both measures have been used even though it is documented that the binary classification system has severe limitations[14,185].

As shown by previous investigators even our study has failed to show any relationship between NP performance and ME events[10]. This is not suprising since until recently there has been no technique available to discriminate between gaseous and particulate ME. The final location in the brain of a microembolus cannot be determined and it may be lodged in an area that cannot be covered by the cognitive tests that we currently use.

There were some unavoidable limitations to this study. We recruited patients from 6 different consultant surgeons and used more than 8 consultant anaesthetists to participated in a standard anaesthetic protocol that could be used during either ICCF or blood cardioplegia technique during myocardial protection. As with the anaesthetist the surgeons had an agreed protocol with regard to using the side-biting clamp during top-end anastomosis.Also there are limitations to the extent once can impose protocols on clinicians however willing they are to participate in trails.Choice of anaesthetic agents may have an influence on the NP outcome as shown in a randomised study by Schoen et al comparing sevoflurane vs propofol during cardiac surgery[224].

There were further limitations in this study which relate to screening of the ascending aorta (a) the use of DP, TOE and EAU to screen the ascending aorta for atheroma and to aid in the modification of the surgical management in a randomised study could have possibly helped in altering the findings leading to no difference in the ME load, or NP outcome. It would have been useful to compare the patients' atheroma load between ICCF and CA groups comparing the severeity of the atheroma grade along with their ME load and final NP deficit outcomes.This was not looked at as there were planning and issues relating to
(b) the 'blinding' of the personnel involved in the atheroma assessment. The surgeons, while performing the DP assessment were blinded to the TOE assessment. When they performed the EAU assessment, although they were blinded to the TOE results, they were

aware of their previous DP assessment. To keep the DP assessor blinded from the EAU assessor involved increasing the 'scrubbed' personnel and was felt to be practically unfeasible in our institution.

In addition some aspects of the study could be criticised.In an attempt to reduce confounding variables we did not recruit patients who had any previous or existing cerebral injury and patients with psychiatric illness.However,it could be argued that by attempting to reduce variables outside our control we may actually excluding the very patients who could potentially benefit from these myocardial protection techniques with regard to NP outcomes.Excluding these types of patients will have reduced further the expected incidence of deficit and will have reduced the statistical power of the study.The strict criteria may also mean that the present study is not representing the whole CABG surgery population and therefore may limit its abilty to generalise from its results.

The aim of any randomized study is to have similar variables between groups. While analysing the intra-operative data the cross-clamp time was found to be significantly longer in the cardioplegia group in comparison to the ICCF technique (Table 6.8). There were also no statistical differences noticed between the detection and generation of ME between the ICCF and cardioplegia group during different surgical events (Table 6.8). It is, therefore, important to note the importance of a randomization study, since most studies especially screening and detecting microemboli have not been properly randomised with recent off-pump techniques[220], epiaortic scanning and using minimal or no touch Y-grafting techniques[101]. Although it is impossible to reach an absolute conclusion from this type of analysis, the fact remains that this is a well powered single institutional study, involving 6 surgeons competent in both cardiac techniques taking part in a randomized study involving a single, stereotyped procedure allowing focus on specific procedural-related issues.

7.7. Conclusion of the study

The null hypotheses tested were:

1) There will be no significant difference in the NP outcome when ICCF or cardioplegia are used as myocardial protection techniques.

2) There will be no significant difference in the ME generated when ICCF or cardioplegia are used.

This study has found the first null hypothesis to be true. No significant difference in NP outcome was found when the ICCF group was compared to the standard cardioplegia group. Any arguments relating to the preferred technique, therefore, should focus on the extent to which these techniques achieve the better form of myocardial protection with least NP deficit.

Using both incidence of deficit and standardized Z change scores, this randomized controlled clinical trial of 195 patients has not found any conclusive evidence of an NP deficit using ICCF when compared to standard cardioplegia technique.

Finally this study provides evidence to suggest that there is no evidence for any difference in the generation of microemboli and neuropsychological outcome differences between these two methods of myocardial protection techniques in an adequately powered and randomized study with well balanced groups is reassuring to those who practise either technique.In particular, it denies concerns regarding intermittent cross-clamp fibrillation, and the strong views that some hold about this technique.

7.8. Suggestions for future studies

As the ageing population of patients undergoing coronary surgery continue to increase along with other co-morbid factors, future studies would be necessary to address and determine the presence of atheromatous lesions in the ascending aorta. This may require a future rich with routine advanced imaging techniques (CT/MRI[231]) prior to using intra-operative epiaortic ultrasonography examination to better evaluate and reduce/prevent cerebral and NP sequelae of ME along with an improved NP testing [225].

Newer Transcranial Doppler techniques may be able to determine the relative pathogenicity of particulate, gaseous and lip ME generated.

The low incidence of NP deficits in this study suggests that future studies will need to either have less strict inclusion criteria or have a greater number of participants requiring a multicentre investigation. There might also be a need to look and refine the existing NP tests by making them more sensitive and should include at the least the core battery as stated in the" Statement of Consensus" and must also should work towards a consensus on the definition of cognitive decline and the definition of control groups[226] .

Finally, given the similarity of effect by cardioplegia and ICCF techniques on generation of NP outcomes, and ME the contemplation of which form of myocardial protection is to be employed should possibly focus more on which method affords more protection to the heart.

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Presentations

1. Cerebral Microemboli in Cardioplegic Arrest and Intermittent Cross-Clamp Fibrillation Suvarna Sujeeth, Stygall Jan, Harrington Jane, S.Newman, Harrison Michael, Walesby Robin, Newman Stanton The Society of Cardiothoracic Surgeons 6th Biennial Meeting. 13-16th June 2003 Kruger National Park, South Africa.

2. Cerebral Microemboli during CABG comparing two Myocardial protection Techniques Sujeeth Suvarna, Jan Stygall, Jane Harrington, Stanton Newman, Michael Harrison, Shyam Kolvekar, Robin Walesby EWCI. 14th Annual Meeting October 23rd –25th 2003, Peratallada, Spain.

3. Screening Ascending aorta: Comparison of Digital palpation, Transoesophageal and Epiaortic Ultrasonography Sujeeth Suvarna, Jan Stygall, Andrew Smith, Robin Walesby, Shyam Kolvekar, Martin Hayward, David Lawrence, Stanton Newman. 3rd EACTS / ESTS Joint Meeting, 12-15 September 2004, Leipzig, Germany.

4. A comparison between Cross-Clamp fibrillation and Cardioplegia: randomised controlled trial- [Oral presentation] Sujeeth Suvarna, Jan Stygall, Michael JG Harrison, Shyam Kolvekar, Robin Walesby, Stanton P Newman. 51st CTCON, 17-20 February 2005, Kochi, India.

5. Neuropsychological outcomes comparing intermittent cross-clamp fibrillation and Cardioplegia during coronary artery bypass surgery. Jan Stygall, Sujeeth Suvarna, Michael JG Harrison, Stanton Newman. September 2006, Colchester,UK

6. Generation of Micro emboli during coronary artery surgery- [Oral presentation] Sujeeth Suvarna, Jan Stygall, Stanton P Newman, Robin Walesby 17th Asian Society of Cardiovascular & Thoracic Society, 5-8th March 2009, Taiwan.

7. Distribution of atheroma in the ascending aorta and its relevance during coronary artery bypass surgery-[Oral presentation] Sujeeth Suvarna, Jan Stygall, Stan Newman. The college of Surgeons of Sri Lanka Annual Academic Session 2009 &The International Conference of the SAARC Surgical Care Society, 26^{th}-29^{th} August 2009, Colombo, Sri Lanka

8. Relevance of atheroma distribution in the ascending aorta using epiaortic Ultrasound during coronary surgery-[Oral presentation] Sujeeth Suvarna, Jan Stygall, Stan Newman 19^{th} World Congress Society of Cardio-Thoracic Surgeons 4^{th}-6^{th} November 2009, Buenos Aires, Argentina

9. Grading of atheroma in the ascending aorta using epiaortic Ultrasound during coronary surgery-[Oral presentation] Sujeeth Suvarna, Jan Stygall, Stan Newman 20^{th} World Congress Society of Cardio-Thoracic Surgeons
20^{th}-6^{th} October 2010, Chennai, India

10. Epiaortic ultrasonography:-Grading of atheroma during coronary arterybypass surgery - [Poster presentation] Sujeeth Suvarna, Jan Stygall,Stan Newman 19^{th} & 21^{st} ASCTVS & ATCSA, May 26^{th}-29^{th} 2011, Phuket, Thailand http://www.ascvts-atcsa2011.org

Chapter 8

Appendices

8.Appendices

8.1.Patient information sheet /Informed consent form

Royal Free and University College Medical School

DIVISION OF MEDICINE
DEPARTMENT OF MEDICINE

Unit of Health Psychology
Head: Professor Stanton Newman

Centre for Cardiovascular Genetics
Centre Director, Professor Steve Humphries FRCPath, MRCP
British Heart Foundation Professor Cardiovascular Genetics

Study contact:
Mrs Jan Stygall
Wolfson Building, 48 Riding House Street
London W1N 8AA
Telephone: (direct line) +44 020 7679 9122

Study contact:
Miss Julie Sanders
The Rayne Institute, 5 University Street, London WC1E 6JJ
Telephone: (direct line) +44 020 7679 6213

CONFIDENTIAL: INFORMATION SHEET (Version 1 02/03)

Title: Comparison of cross-clamp fibrillation and cardioplegia technique in coronary artery bypass graft surgery on microemboli, neuropsychology and inflammatory response.
Investigators: Prof. S Newman, Mr R Walesby, Prof. M Mythen, Mr Chandrakumar, Dr A Campbell, Dr P Wallman, Dr H Montgomery, Prof. S Humphries, Miss J Sanders, Mrs J Stygall.

As a patient of University College Hospitals Trust we invite you to participate in this research study. This help will **NOT** involve taking any drugs or medications. **You do not have to take part in this study if you do not want to. If you decide to take part you may withdraw at any time without giving a reason. Your decision whether to take part or not will not affect your care and management in any way.**

Background
AT UCL/UCLH we are interested in finding out more about coronary artery bypass surgery and how we can improve patient care in the future. Currently we are looking at three aspects of particular importance.

a) *The effects of intermittent cross-clamp fibrillation and cardioplegia on cognitive function and myocardial protection.*
It will have been explained to you that it is necessary to stop the heart in order to perform surgery. There are two alternative techniques used to stop the heart. One uses a strong potassium solution and the other interrupts the blood supply to the heart. Both techniques appear to be equally safe. Studies have shown that one quarter of patients who have heart surgery may have a slight impairment in their concentration and memory afterwards. We are interested in finding out whether either of the two techniques of stopping the heart are better at protecting the heart and brain and also have any affect on quality of life.

b) the role of interleukin-6 and beta-fibrinogen genotype and the acute phase response to coronary artery bypass grafting
Many aspects of our health are at least in part genetically controlled. Genes encode the information that determines how our bodies function. At UCL/UCLH, we are trying to understand the role of genes in heart disease. We are particularly interested in genes called interleukin-6 (IL-6) and beta-fibrinogen and finding out whether the differences in these genes affect the body's normal healing response following coronary artery bypass surgery. To find these differences, we need to look at many samples of DNA (the 'code-strips' on which genes are found), to look for differences between people and how this affects their healing process following surgery.

c) *combined effects*
In addition to answering each of the questions above there could also be links between these two aspects of coronary artery bypass surgery. We think there could be differences in the healing response to the surgery depending on which technique is used to stop the heart. We are also interested in finding out whether genetic differences are important in protecting the heart and brain and have an affect on quality of life following coronary artery bypass graft surgery.

What is involved?

a) *The effects of intermittent cross-clamp fibrillation and cardioplegia on cognitive function and myocardial protection.*
To find out if the technique used to stop your heart during the operation affects your memory and concentration we need to conduct some tests before and after your operation. On admission to hospital you will be asked to complete some tasks of memory and concentration which involve drawing on paper and pressing buttons on a computer. You will also be asked to fill in the questionnaires relating to your mood state and quality of life. This whole assessment will take about an hour. Approximately 6 weeks after your operation, whether or not you take part in this study, you will return to outpatients for a check-up. If you agree to participate in this study, you will return to outpatients for a check-up. If you agree to participate in the study, the memory and concentration tests will be repeated at this visit.

During your operation we would also like to monitor the blood flow to your brain and examine your heart. This will be done in addition to the usual treatment and monitoring you will receive. A Doppler ultrasound will be used to measure the blood flow to your brain. Ultrasound is harmless probes placed on the skin similar to the test pregnant women routinely receive. A Trans-oesophageal probe will be put down the gullet to obtain pictures of the heart. This is a commonly used technique to examine the heart and its valves. As part of routine monitoring, a canula will be placed in an artery in the wrist to measure blood pressure. If you are in this study extra information will be obtained by injecting contrast material through this canula.

b) *the role of interleukin-6 and beta-fibrinogen genotype and the acute phase response to coronary artery bypass grafting*
In order to look at the effect of your IL-6 and beta-fibrinogen genes on your healing process following your operation we would like to take six blood samples, additional to the routine blood tests you will have. The first (15ml) will be taken on admission. If you require routine blood samples for your operation, they will be done at the same time to avoid you having more than one blood test. Two samples will be taken while you are undergoing surgery (10ml each). A further two samples will be taken approximately 4 and 24 hours after your operation (10 ml each). These blood tests will be taken via the canula inserted during the operation in the artery in your wrist and hence will be painless. A final 10 ml sample will be taken 48 hours after your operation. We would also like permission to monitor your recovery after the operation while you are in hospital and can do this from your medical notes.

For us to answer all our questions we would like to invite you take part in both parts of the study. However, you are free to decide to take part in both, one, or neither of them.

Protection of information and confidentiality
All the information we obtain will be strictly confidential. University College London will overview the collection, storage and handling of the data and Professor Newman, in his capacity of principal investigator, will be responsible for security and access to the data. Only study investigators (named above) will have access to the data. The information collected during the study, with exception of

your name, will be stored and analysed confidentially in a computer. No identifiers on the data held by computer will enable a third party to link the data to you. A study ID number will be assigned to you and this will appear on all data including blood samples, medical information and questionnaires. Under all circumstances and at all times all data will be kept strictly confidential and secured under lock and key in UCL. The data will be stored for 5 years after the study has been completed. Information about you or your genes is bound by the regulations of medical confidentiality and will not be made available to outside organisations or insurance companies. If the results are published in medical journals your individual details will not be revealed. Copies of the publications will be available to you from the researchers.

Risks
Your surgeon will explain to you the usual risks involved with your type of heart surgery. Both types of myocardial protection techniques used in this study have been used before and no clinically significant adverse effects have been found. The risks of taking part in the study are so small as to be undetectable.
The taking of the first blood sample may be briefly uncomfortable. The other two blood samples via the canula will be painless. There are **no risks** involved in taking part in this part of the study.

Benefits
As with many clinical research projects the benefits will really be for patients in the future when we have answered our questions.

Ethics Committee Review
All proposals for research using human subjects are reviewed before an ethics committee before they can proceed. This proposal was reviewed by the Joint UCL/UCLH Ethics Committee in Ethics of Human Research.

Royal Free and University College Medical School
UNIVERSITY COLLEGE LONDON MEDICAL SCHOOL
DIVISION OF MEDICINE
DEPARTMENT OF MEDICINE

Unit of Health Psychology
Head: Professor Stanton Newman

Centre for Cardiovascular Genetics
Centre Director: Professor Steve Humphries, FRCPath, MRCP
British Heart Foundation Professor of Cardiovascular Genetics

Study contact:
Ms Jan Stygall
Wolfson Building, 48 Riding House Street,
London W1N 8AA
Telephone (Direct Line): +44 020 7679 9122
e-mail: j.stygall@ucl.ac.uk

Study Contact:
Miss Julie Sanders
The Rayne Institute, 5 University Street, London WC1E 6JJ
Telephone (Direct Line): (+44) 020 7679 6213
e-mail: j.sanders@ucl.ac.uk

CONFIDENTIAL: CONSENT FORM (Version 1, 02/03)
UCLH project ID 01/ 0261 , 99/ 0099

Title: Comparison of cross-clamp fibrillation and cardioplegia technique in coronary artery bypass graft surgery on microemboli, neuropsychology and inflammatory response.
Investigators: Prof S. Newman, Mr R Walesby, Prof M Mythen, Mr Chandrakumar, Dr A Campbell, Dr P Wallman, Dr H Montgomery, Prof S Humphries, Miss J Sanders, Mrs J Stygall.

To be completed by participant **Delete as necessary**

1. Have you read the information sheet? YES/NO

2. Have you had the opportunity to ask questions and discuss the study? YES/NO

3. Have you received satisfactory answers to all your questions? YES/NO

4. Have you received enough information about this study? YES/NO

5. Which investigator(s) named above on this sheet have spoken to you about this study?

....

6. Do you understand that you are free to withdraw from the study and /or ask for your sample to be destroyed

- at any time
- without giving a reason
- without affecting your future medical care YES/NO

7. Do you agree to take part in the

Memory, concentration and quality of life study? YES/NO

Genetics study (blood)? YES/NO

8. If we receive the approval of the ethics committee, and were to treat your blood sample in the same way, would you let us (in the future) look at how genes relate to other diseases? YES/NO

9. If, yes may we do this without contacting you again for written permission? YES/NO

Participant's signature................................ .... Date...................

Participant's name (please print)..

Investigator's signature .... Date..................

If you have any comments or concerns you may discuss these with the research investigator, if you wish to go further and complain about any aspect of the way you have been treated during the course of the study, you should write or get in touch with the Complaints Manager, UCL hospitals. Please quote the UCLH project ID at the top of this consent form.

8.2. Subjective assessment questionnaire

SELF-EVALUATION QUESTIONNAIRE

Developed by Charles D. Spielberger
in collaboration with
R.L. Gorsuch, R. Lushene, P.R. Vagg, and G.A. Jacobs

STAI Form Y-1

Name: ______________________ Date: __________ S _____

Age: ____________ Sex: M ______ F ______ T _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you feel *right* now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

		NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1.	I feel calm	1	2	3	4
2.	I feel secure	1	2	3	4
3.	I am tense	1	2	3	4
4.	I feel strained	1	2	3	4
5.	I feel at ease	1	2	3	4
6.	I feel upset	1	2	3	4
7.	I am presently worrying over possible misfortunes	1	2	3	4
8.	I feel satisfied	1	2	3	4
9.	I feel frightened	1	2	3	4
10.	I feel comfortable	1	2	3	4
11.	I feel self-confident	1	2	3	4
12.	I feel nervous	1	2	3	4
13.	I am jittery	1	2	3	4
14.	I feel indecisive	1	2	3	4
15.	I am relaxed	1	2	3	4
16.	I feel content	1	2	3	4
17.	I am worried	1	2	3	4
18.	I feel confused	1	2	3	4
19.	I feel steady	1	2	3	4
20.	I feel pleasant	1	2	3	4

Distributed in the UK and Ireland by Oxford Psychologists [illegible]

8.3. Individual case report form

INDIVIDUAL CASE REPORT FORM

CROSS-CLAMP FIBRILLATION Vs CARDIOPLEGIA STUDY

A Study to examine the effects of intermittent Cross-clamp fibrillation and Cardioplegia on neuropsychological outcomes and myocardial protection

Patient Initials	Trial No.

Hospital No.	Consultant

Telephone number..

Principal Investigators

Mr RK Walseby
Heart Hospital
West moreland St
London
W1N 8AA

Professor SP Newman
Middlesex Hospital
Mortimer St
London
W1N 8AA

Professor MG Harrison
Middlesex Hospital
Mortimer St
London
W1N 8AA

Dr S Wright
Middlesex Hospital
Mortimer St
London
W1N 8AA

Research team

Mr.S Chandrakumar
Heart Hospital
Westmoreland St
London

Dr.A Campbell
Heart Hospital
West moreland St
London

Mrs J Stygall
Middlesex Hospital
Mortimer St
London

(If found, please return to Sujeeth cKumar, Dept of Cardiac Surgery, Heart Hospital – 020 757 38888)

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

Assessment Dates

Assessment 1
Outpatient or Inpatient

Prior to scheduled surgery date

d	d	m	m	y	y

Assessment 2
Inpatient

Intra-operative

d	d	m	m	y	y

Assessment 3
Inpatient

Post -operative

d	d	m	m	y	y

Assessment 4
Outpatient

Post -operative

d	d	m	m	y	y

Assessment 1
Inpatient or Outpatient prior to surgery

- Informed Consent
- Demographic Data
- General Medical History
- Cardiovascular History
- Parsonnet Score
- General Clinical Exam
- Neurological Exam
- Neuropsychological Testing
- ECG and CXR

INCLUSION CRITERIA

	Yes	No
1.Able to speak and read English	( )	( )
2.Age	( )	( )
3.CABG only	( )	( )
4.No history of TIA OR CVA	( )	( )
5.No history of renal failure	( )	( )
6.Has signed the consent form	( )	( )
7.Is not enrolled in another study	( )	( )

NOTE
IF ANY "NO" BOX IS TICKED, THE PATIENT IS NOT ELIGIBLE FOR THE STUDY

Is the patient eligible for the study? Yes No

If yes,

***Complete details of scheduled date of surgery and assessment dates at front of file.**

***Inform Perfusionists**

***Inform Anaesthetists (theatre list)**

***Continue with demographics and medical exam.**

DEMOGRAPHICS

Date of Birth ___/___/___. Age _______. Sex ☐ male ☐ female Years of Education _____. (5 onwards)	Race	c b a o os	caucasian black asian oriental other, specify ....

Height (m)		Weight (kg)		BMI	

GENERAL MEDICAL HISTORY

Enter any significant medical/surgical history

☐ Tick if none

DESCRIPTION	DATE OF ONSET	DATE CEASED

MEDICATION	DOSE

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Elective | urgent

CARDIOVASCULAR HISTORY

EVENT	YES	NO	START DATE						FINISH DATE					
Stable Angina	grade:		D	D	M	M	Y	Y	D	D	M	M	Y	Y
Unstable Angina	grade:		D	D	M	M	Y	Y	D	D	M	M	Y	Y
Myocardial Infarction			D	D	M	M	Y	Y	D	D	M	M	Y	Y
Dyspnoea	grade:		D	D	M	M	Y	Y	D	D	M	M	Y	Y
Angiogram			D	D	M	M	Y	Y	D	D	M	M	Y	Y
Angioplasty or Stenting			D	D	M	M	Y	Y	D	D	M	M	Y	Y
HYPERTENSION			D	D	M	M	Y	Y	D	D	M	M	Y	Y
LV Aneurysm			D	D	M	M	Y	Y	D	D	M	M	Y	Y
Peripheral Vascular Disease			D	D	M	M	Y	Y	D	D	M	M	Y	Y
Time of Angio	months ago :													
Time on waiting list	Months:													
? Working at present														

If Not working, due to 1)normal retirement pre-symptoms, 2)early retirement due to symptoms or 3)off sick due to symptoms

Smoker	Yes	No	Ex	PACK YEARS	D	D	M	M	Y	Y	D	D	M	M	Y	Y
					D	D	M	M	Y	Y	D	D	M	M	Y	Y

EJECTION FRACTION	Good (>50%)	Moderate (30-49%)	Poor (<30%)

LMS Normal

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PARSONNET SCORE		
Female	1	
Obesity (BMI > 30)	3	
Diabetes	3	
Hypertension (Systolic BP > 140mmHg)	3	
Ejection Fraction Good (>50%)	0	
Mod (30-49)	2	
Poor (<30%)	4	
Age 70-74	7	
75-79	12	
80 +	20	
Re-operation First	5	0
Second	10	0
Pre-operative IABP	2	
Left Ventricular Aneurysm	5	
Emergency Surgery	10	0
Dialysis Dependency	10	0
Catastrophic States	10-50	0
Other Rare Circumstances (eg severe asthma)	2-10	
Valve Surgery	N/A	0

Total	

EURO SCORE   Logistic | Standard

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GENERAL PHYSICAL EXAM

SYSTEM	NORMAL	ABNORMAL	NOT KNOWN
1.CARDIOVASCULAR			
? CAROTID BRUITS			
2.RESPIRATORY			
3.GI			
4.MUSCULOSKELETAL			
5.URINALYSIS			
6.ENDOCRINE			

DETAILS OF ABNORMALITIES FOUND	
SYSTEM NO.	FINDINGS

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NEUROLOGICAL EXAM

SYSTEM	RUL	RLL	LUL	LLL
TONE				
POWER				
CO-ORDINATION				
REFLEXES				
SENSATION				

DETAILS OF ABNORMALITIES FOUND

SYSTEM	FINDINGS

CRANIAL NERVES	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
NORMAL												
ABNORMAL												

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

ECG

INTERPRETATION

Within normal limits ☐

Significantly abnormal ☐ If abnormal, describe below

....

....

CXR

INTERPRETATION

Within normal limits( ) ☐

Significantly abnormal ☐ if abnormal, describe below

....

....

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

NEUROPSYCHOLOGICAL TESTS

NART	

Rey Auditory Verbal Learning Test							
Score	1:	2:	3:	4:	5:	6:	7:

Trail Making Test A		Trail Making Test B	
Time to Completion		Time to Completion	

Grooved Pegboard Test	
Time to Completion,dominant hand	
Time to Completion,non-dominant hand	

Symbol Digits Modalities Test			
Total time		Number correct answers	

Non-verbal Memory Test			
Number correct		Time to completion	

Letter Cancellation Test			
Number of Intrusion Errors Made			
Number of targets missed		Time to completion	

Choice Reaction Time Test			
A Accuracy		A Time	
B Accuracy		B Time	

Speilberger state		Speilberger trait	
CESD			

SF – 36

Q1 ( )

Q2 ( )

Q3 a( ) b( ) c( ) d( ) e( ) f( ) g( ) h( ) i( ) j( )

Q4 a( ) b( ) c( ) d( )

Q5 a( ) b( ) c( )

Q6 ( )

Q7 ( )

Q8 ( )

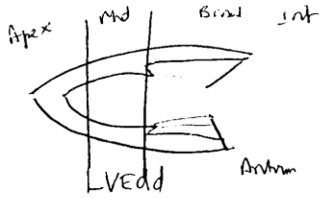
Q9 a( ) b( ) c( ) d( ) e( ) f( ) g( ) h( ) i( ) j( )

Q10 a( ) b( ) c( ) d( )

Assessment 2

Inpatient – intra-operative

- Transcranial Doppler Data
- TOE
- Cardiac output
- Anaesthesia Protocol Check
- Intra-operative Vital Signs
- Record of Intra-operative Events



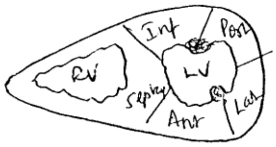
LVEds

EF

FS%

TOE

PRE-BYPASS

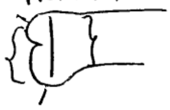


L V FUNCTION

E/A ratio:

E : A

Proximal Aorta



m mode:

EU

0 (N)
1
2
3

EPI-AORTIC SCAN

3 SEGMENTS	Descending Aorta
PROXIMAL	Prox ○
MIDDLE	Mid ○
DISTAL	distal ○

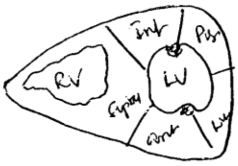
Palpation: ABSENT | PRESENT

POST-BYPASS

L V FUNCTION

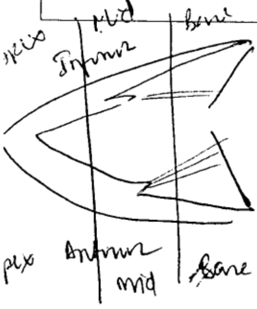
E/A ratio:

m mode:



LVEdd

LVEds



E : A

Post CPB :

Inotropes . Yes | No

Cannulation site Yes | No

CARDIAC OUTPUT

To be inserted

NOT DONE

START (KNIFE TO SKIN)		FINISH (SKIN CLOSURE)		OP TIME	
STERNOTOMY					

TRANSCRANIAL DOPPLER

TRACE OBTAINED	RIGHT	Good Mod Poor	LEFT	Good Mod Poor	NEITHER	
DEPTH		POWER		GAIN		

TIME	ACTUAL TIME	MCA BLOOD VELOCITY
Pre CPB (just before cannulation)		
Pre-CPB (immed prior to CPB)		
During CPB (15mins into CPB)		
Post-CPB (10mins after stopping)		

TIME	MICROEMBOLI COUNT
For 15mins after sternotomy	
During CPB	
Post CPB	
Total count	

INTRA-OP VITAL SIGNS

TIME		MAP	SBP	DBP	TEMP
	Pre-induction				
	Post-induction				
	Pre-sternotomy				
	Post-sternotomy				
	Pre-CPB				
	Post-CPB				
	Post-skin closure				

ON CPB		OFF CPB		TOTAL CPB TIME	
NO. OF GRAFTS		TOTAL CROSS CLAMP TIME		? LIMA YES/NO	
INDIVIDUAL CROSS CLAMP TIMES	ON OFF TIME	ON OFF TIME	ON OFF TIME	ON OFF TIME	
CLINICAL SIGNS OF AORTIC ATHEROMA OR CALCIFICATION	YES		NO		
METHOD OF CANNULATION SIDE CLAMP OR NOT?	YES		NO		
TIME OF CANNULATION			TIME OF DE-CANNULATION		

Cx ✓ x | CBR ✓ x

CARDIOPLEGIA	
TOP END CLAMP on off /	Top end on off
Top end on off	
Top end clamp on off	Top end on off
TIME OF START OF REWARM	
TIME TAKEN TO REACH 37ºC FROM MINIMUM	

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Assessment 3

Inpatient – immediately post op until discharge

- **Cardiac output**
- **Neurological Exam**
- **ASEPSIS wound infection score**
- **Adverse Events and Complications**

NEUROLOGICAL EXAM

SYSTEM	RUL	RLL	LUL	LLL
TONE				
POWER				
CO-ORDINATION				
REFLEXES				
SENSATION				

DETAILS OF ABNORMALITIES FOUND

SYSTEM	FINDINGS

CRANIAL NERVES	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII
NORMAL												
ABNORMAL												

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

CARDIAC OUTPUT

To be inserted

NOT DONE

ECG

INTERPRETATION

Within normal limits ☐

Significantly abnormal ☐ If abnormal, describe below

....

....

CXR

INTERPRETATION

Within normal limits( ) ☐

Significantly abnormal ☐ if abnormal, describe below

....

....

ASEPSIS WOUND INFECTION SCORE

To be inserted

NOT DONE

COMPLICATIONS(Prior to discharge)					
CARDIOVASCULAR					
MI		Arrest		AF	
Early bleed		Late bleed		Tamponade	
Pericarditis		Low cardiac output			
RESPIRATORY					
Resp failure		Resp arrest		ARDS	
Pleural effusion		Infection		Pulm embolus	
Bronchoconstriction		Basal collapse		Re-intubation	
Pneumothorax		Tracheostomy			
GASTROINTESTINAL					
Peptic ulceration		Pancreatitis		Ischaemic bowel	
RENAL					
Haemolysis		Mild failure(Cr<200)		Filtration/dialysis	
NEUROLOGICAL					
TIA		CVA		Post pump psychosis	
OTHER					
Multisystem failure		Operative death		Unexplained post op death	

DATE OF DISCHARGE	
AT DAY NO	

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Assessment 4
Out-patient at 6 weeks

- **Neuropsychological Tests**
- **Outpatient Assessment**

SUBJECTIVE COGNITION SCALE			
Since your operation are you:	**More**	No Change	**Less**
More or less alert and thinking more or less clearly			
Forgetting things, for example, things that have happened recently, where you put things or keeping appointments			
Have more or less minor accidents, for example dropping things, tripping			
Reacting more or less quickly to things that are said or done			
Having more or less difficulty in solving problems and learning new things			
Having more or less difficulty in making decisions			
Able to keep your attention to a task for more or less time			
Making more or less mistakes			
Having more or less difficulty in doing things which involve thought and concentration			

NEUROPSYCHOLOGICAL TESTS

Rey Auditory Verbal Learning Test							
Score	**1:**	**2:**	**3:**	**4:**	**5:**	**6:**	**7:**

Trail Making Test A		Trail Making Test B	
Time to Completion		Time to Completion	

Grooved Pegboard Test	
Time to Completion,dominant hand	
Time to Completion,non-dominant hand	

Symbol Digits Modalities Test			
Total time		Number correct answers	

Non-verbal Memory Test			
Number correct		Time to completion	

Letter Cancellation Test			
Number of Intrusion Errors Made			
Number of targets missed		Time to completion	

Choice Reaction Time Test			
A Accuracy		A Time	
B Accuracy		B Time	

Speilberger state		**CESD**	

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

SF36

1) __

2) __

3) a) __ b) __ c) __ d) __ e) __ f) __ g) __h) __ i) __ j) __

4) a) __ b) __ c) __ d)

5) a) __ b) __ c) __

6) __

7) __

8) __

9) a) __ b) __ c) __ d) __ e) __ f) __ g) __ h) __ i) __ j) __

10) a) __ b) __ c) __ d) __

OUTPATIENT ASSESSMENT

SYMPTOMS Angina Yes ☐ No☐ SOB Yes ☐ No☐

WOUND Sternal

Leg/Forearm

HOSPITAL READMISSION Yes ☐ No☐

OTHER PROBLEMS

CXR

ECG

CURRENT MEDICATION

PLAN

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

CORONARY ARTERY BYPASS SURGERY

Age
Sex
BMI
Urgency of operation
Prior cardiac operation
Angina class
History of MI
Smoking
Diabetes
Hypercholestremia
Peripheral vascular disease
CVDisease
Respiratory Disease
Renal dysfunction
Extent of coronary disease
Ejection fraction

MYOCARDAL PROTECTION

TOTAL COUNT

UCL HOSPITALS, MORTIMER STREET, LONDON W1N 8AA

3-Techniques(Atheroma)		
PALPATION	**TOE**	**EPI-AORTIC**
1)Yes Thickening	1)Mild <1mm YES / NO	1)Mild YES/ NO
2)No Thickening	2)Moderate 1-2mm YES / NO	2)Moderate YES / NO
	3)Severe >3mm YES / NO	3)Severe YES / NO

EU

PROXIMAL | MIDDLE | DISTAL

Change of surgical technique	
YES	**NO**

Inotropes yes /No

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